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(71) Applicant (*for all designated States except US*): INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): TANG, Y., Tom [CN/US]; 4230 Ranwick Court, San Jose, CA 95118 (US). CORLEY, Neil, C. [US/US]; 1240 Dale Avenue #30, Mountain View, CA 94040 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA 95054 (US). YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive #12, Mountain View, CA 94040 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US).

(74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).

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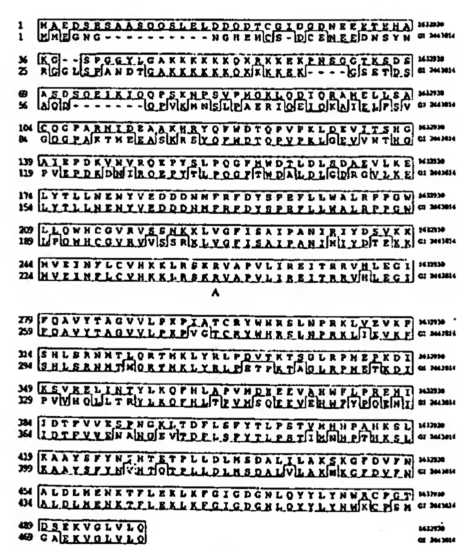
(54) Title: HUMAN TRANSFERASE PROTEINS

(57) Abstract

The invention provides human transferase proteins (TRNSFS) and polynucleotides which identify and encode TRNSFS. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of TRNSFS.



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HUMAN TRANSFERASE PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of human transferase proteins and to the use of these sequences in the diagnosis, treatment, and prevention of cancer, developmental disorders, gastrointestinal disorders, genetic disorders, immunological disorders, neurological disorders, reproductive disorders, and smooth muscle disorders.

BACKGROUND OF THE INVENTION

Transferase Proteins

Transferases are enzymes that catalyze the transfer of molecular groups from a donor to an acceptor molecule. The reaction may involve an oxidation, reduction, or cleavage of covalent bonds and is often specific to a substrate or to particular sites on a type of substrate. Transferase proteins participate in reactions essential to such functions as synthesis and degradation of cell components, and regulation of cell functions, including cell signaling, cell proliferation, inflammation, apoptosis, secretion and excretion. Transferases are involved in key steps in disease processes involving these functions. These enzymes are frequently classified according to the type of group transferred. For example, methyl transferases transfer one-carbon methyl groups, amino transferases transfer nitrogenous amino groups, and similarly denominated enzymes transfer aldehyde or ketone, acyl, glycosyl, alkyl or aryl, isoprenyl, saccharyl, phosphorous-containing, sulfur-containing, or selenium-containing groups, as well as small enzymatic groups such as Coenzyme A.

One example of a glycosyl transferase is O-linked N-acetylglucosamine (O-GlcNAc) transferase, an enzyme that catalyzes the reaction of monosaccharide N-acetylglucosamine linking to the hydroxyl group of a serine or threonine residue. O-GlcNAc and N-acetyl-β-D-glucosaminidase (O-GlcNAcase), regulate the attachment and removal, respectively, of O-GlcNAc from proteins in a manner analagous to regulation of protein phosphorylation by kinases and phosphotases. O-GlcNAc transferase has been localized primarily in the nucleus and the cytosol of cells and has been shown to play a role in several cellular systems such as transcription, nuclear transport, and cytoskeletal organization. O-GlcNAc transferase is a heterodimer consisting of two catalytic 110-kDa (p110) subunits and one 78-kDa (p78) subunit. The gene encoding this enzyme is highly conserved. The amino terminus of the p110 subunit has homology to the tetratricopeptide repeat (TPR) motif, while the carboxyl terminus has no significant homology

(Kreppel, L.K. et al. (1997) J. Biol. Chem. 272:9308-9315). Proteins containing the TPR motif interact through this TPR domain to form regulatory complexes. TPR motifs are believed to play a role in modulation of cellular processes such as cell cycle, transcription, and protein transport (Das, A.K. et al. (1998) EMBO J 17:1192-1199).

The enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) is a purine salvage enzyme that catalyzes the conversion of hypoxanthine and guanine to their respective mononucleotides. HGPRT is ubiquitous, is known as a 'housekeeping' gene, and is frequently used as an internal control for reverse transcriptase polymerase chain reactions. There is a serine-tyrosine dipeptide that is conserved among all members of the HGPRT family and is essential for the phosphoribosylation of purine bases (Jardim, A. and Ullman, B. (1997) J. Biol. Chem. 272:8967-8973). A partial deficiency of HGPRT can lead to overproduction of uric acid, causing a severe form of gout. An absence of HGPRT causes Lesch-Nyhan syndrome, characterized by hyperuricaemia, mental retardation, choreoathetosis, and compulsive self-mutilation (Sculley, D.G. et al. (1992) Hum Genet 90:195-207).

Polyprenyl transferases catalyze the addition of polyprenyl groups to molecules. For example, the enzyme 1,4-dihydroxy-2-napthoate octaprenyltransferase catalyzes the conversion of the soluble 1,4-dihydroxy-2-napthoic acid (DHNA) to the membrane-bound demethylmenaquinone by attaching a 40-C side chain to DHNA, a key step in the biosynthesis of menaquinone (vitamin K2). This octaprenyltransferase is a membrane protein in Escherichia coli that is necessary for the synthesis of menaquinone (Suvarna, K. et al. (1998) J. Bacteriol. 180:2782-2787). Quinones, in many cases, take part in the oxidation-reduction cycles essential to living organisms (Morrison, R.T. and Boyd, R.N. (1987) Organic Chemistry, Allyn and Bacon, Inc., Newton, Massachusetts, pp. 1092-1093). Other octaprenyltransferases have been shown to allow the synthesis of quinones under anaerobic conditions and, therefore, may play a role in anaerobic metabolism (Alexander, K. and Young, I.G. (1978) Biochemistry 17:4750-4755).

The synthesis of 3'-phosphoadenosine-5'-phosphosulfate (PAPS) requires two enzymes, adenosine triphosphate (ATP) sulfurylase and adenosine 5'-phosphosulfate (APS) kinase. ATP sulfurylase catalyzes the formation of APS from ATP and free sulfate. APS kinase phosphorylates APS to produce PAPS, the sole source of donor sulfate in higher organisms. In bacteria, fungi, yeast, and plants, these two enzymes are separate polypeptides. In animals, ATP sulfurylase and APS kinase are present in a single protein. The bifunctional enzyme found in mammals shows extensive homology to known sequences of both ATP sulfurylases and APS kinases. APS kinase peptide sequences are well conserved and contain an ATP-GTP binding motif (P-loop) flanked by cysteine residues and a PAPS-dependent enzyme motif. ATP sulfurylase peptide sequences have

a PP-motif found in ATP sulfurylases and PAPS reductases (Rosenthal, E. and Leustek, T. (1995) Gene 165:243-248; Li, H. et al. (1995) J. Biol. Chem. 270:29453-29459; Deyrup, A.T. et al. (1998) J. Biol. Chem. 273:9450-9456; Bork, P. and Koonin, E.V. (1994) Proteins 20:347-355).

The enzyme phosphatidylethanolamine N-methyltransferase (PEMT) catalyzes the methylation of phosphatidylethanolamine. Hepatocytes in the liver synthesize phosphatidylcholine (PC) by stepwise methylation of phosphatidylethanolamine and have abundant activity for PEMT. Other cells and tissues express minimal activities for PEMT. All mammalian cells, including hepatocytes, synthesize PC from choline via the CDP-choline pathway. Evidence suggests that one function of hepatic PEMT is to maintain PC synthesis and generate choline when dietary supply of choline is insufficient, as occurs during pregnancy, lactation, or starvation (Walkey, C.J. et al. (1998) J. Biol. Chem. 273 :27043-27046). Forms of PEMT may also play a role in hepatocyte proliferation and liver cancer (Walkey, C.J. et al. (1999) Biochim. Biophys. Acta 1436:405-412). In the brain, decreased PEMT activity has been associated with Alzheimer's disease (Guan, Z.Z. et al. (1999) Neurochem. Int. 34:41-47).

Sulfotransferase enzymes catalyze the transfer of sulfur-containing groups to molecules. For example, HNK-1 sulfotransferase (HNK-1ST) forms the HNK-1 carbohydrate epitope by adding a sulfate group to glycoproteins and glycolipids. The HNK-1 epitope was discovered by an antibody against human natural killer cells and is found in neural adhesion molecules, including N-CAM and myelin-associate glycoprotein. The HNK-1 carbohydrate epitope was recognized to have functional significance as an auto-antigen involved in peripheral demyelinative neuropathy. The HNK-1ST is a type II membrane protein with a consensus sequence shared by Golgi-associated sulfotransferases. The human and rat HNK-1STs share 90% homology in amino acid sequence. Human HNK-1ST was predominantly detected in fetal brain and in adult brain, testis, and ovary. (See Ong, E. et al. (1998) J. Biol. Chem. 273:5190-5195.)

Carnitine palmitoyltransferase I (CPT I) is an enzyme that catalyzes the transfer of fatty acyl groups from coenzyme A to carnitine, the rate-determining step in mitochondrial fatty acid β-oxidation (a major source of energy production in the cell). CPT I has two structural genes (α and β) that are differentially expressed in tissues that utilize fatty acids as fuel. The α structure is expressed most highly in the liver, pancreatic β cells, and heart. The β structural gene of CPT I is predominately expressed in skeletal muscle, adipose tissue, heart, and testis (Yu, G.S. et al. (1998) J. Biol. Chem. 273:32901-32909). CPT I deficiency is a life-threatening disorder that appears to be treatable with medium-chain triglycerides. The disorder first presents, between 8 and 18 months, with Reye syndrome-like episodes associated with fasting due to viral infection or diarrhea. Coma, seizures, hepatomegaly, and hypoketotic hypoglycemia characterize these

episodes. Persistent neurological defects are common (Online Mendelian Inheritance in Man entry #255120; ExPASy Enzyme:EC 2.3.1.21).

The enzyme glycine N-methyltransferase catalyzes the transfer of the methyl group from S-adenosylmethionine to glycine to form S-adenosylhomocyteine and sarcosine. Glycine N-methyltransferase is a tetramer of identical subunits, has a nucleotide binding region, and is localized in the liver. Amino acid sequence homology is found between glycine N-methlytransferases from rat, rabbit, pig, and human livers. Glycine N-methyltransferase can exist as a dimer which binds polycyclic aromatic hydrocarbons (PAHs) and acts as a transcriptional activator (Ogawa, H. et al. (1998) Int. J. Biochem. Cell Biol. 30:13-26; Bhat, R. and Bresnick, E. (1997) J. Biol. Chem. 272:21221-21226).

Myristoyl CoA:protein N-myristoyl-transferase

N-acylation with the 14-carbon fatty acid, myristate is found on the amino groups of N-terminal glycines of a number of proteins that are essential to normal cell functioning and/or are potential therapeutic targets of disease. Examples of such proteins include subunits of heterotrimeric G proteins, GTP-binding arf1, human immunodeficiency virus gag and nef proteins, myristolated alanine-rich C kinase substrate (MARCKS), the protein phosphatase calcineurin B, the pp60^{src} protein tyrosine kinase, the retinal calcium-binding recoverin, the caveolae-associated endothelial nitric oxide synthase, the catalytic subunit of cAMP-dependent protein kinase, and mitochondria-associated cytochrome b5 reductase. (Glover, C.J. et al. (1997) J. Biol. Chem. 272:28680-28689.) N-myristoylated proteins are associated with a variety of organelles with the myristate moiety required for such diverse functions as specific protein-protein or protein-lipid interactions, ligand-induced protein conformational changes, and correct subcellular targeting.

Protein myristoylation occurs almost exclusively cotranslationally during protein synthesis of the first 100 amino acids. The reaction is catalyzed by the enzyme myristoyl CoA:protein N-myristoyl-transferase (NMT) 1 (EC 2.3.1.97). (Towler, D. A. et al. (1987) Proc. Natl. Acad. Sci. 84:2708-2712.) Immunofluorescence microscopy reveals NMT to be distributed uniformly throughout the cytoplasm of yeast and mammalian cells. This finding, plus evidence that N-myristoylation occurs on nascent polypeptides bound to free polyribosomes, establish that NMT is physically localized and functionally active in the cell cytoplasm. (Wilcox, C. et al. (1987) Science 238:1275-1278.)

Protein N-myristoylation appears to be a tightly regulated process involving i) the coordinated participation of several different enzymes/proteins, e.g. N-methionylaminopeptidase, fatty acid synthetase, long chain acyl-CoA synthetase, acyl-CoA-binding proteins; ii) access of NMT to pools of myristoyl-CoA substrate; and iii) N-myristoylation of nascent polypeptide

substrates during protein synthesis to avoid potential interfering reactions such as N-acetylation and polypeptide folding. The ability of NMT to function in regulated N-myristoylation has implied the existence of mechanisms designed to ensure targeting of NMT to the appropriate protein synthesis machinery. These mechanisms may involve interactions with other cooperating components that facilitate the recognition and efficient N-myristoylation of the rapidly growing polypeptide substrates. (Glover, et al. supra.) Protein N-myristoylation activity may be a chemotherapeutic target for cancer, infectious diseases, and immune disorders. Antagonists of NMT may reduce posttranslational myristoylation of oncoproteins and other growth-activating cellular proteins. (Felsted, R.L. et al., (1995) J. Natl. Cancer Inst. 87:1571-1573; Furuishi, K. et al., (1997) Biochem. Biophys. Res. Comm. 237:504-511.)

Mannose-1-phosphate guanyltransferase

Many secretory proteins and membrane proteins are glycosylated proteins that have covalently attached carbohydrate chains, or oligosaccharides. Some of these glycoproteins have only one or a few carbohydrate groups while others have numerous oligosaccharide side chains, which may be linear or branched. The sugar residues of many plasma membrane glycoproteins orient these proteins in membranes. Sugar residues of glycoproteins are hydrophilic and strongly prefer to be located near the aqueous or extracellular surface rather than the hydrocarbon core of the plasma membrane. Because there is a high energy barrier to the rotation of a glycoprotein from one side of the membrane to the other, the carbohydrate groups of membrane glycoproteins help to maintain the asymmetric character of biological membranes. One of the best-characterized glycoproteins is glycophorin, a protein found in the membrane of red blood cells. Many soluble glycoproteins are known as well, including carrier proteins, antibodies, and many of the proteins contained in lysosomes. Carbohydrate groups of plasma membrane glycoproteins play a major role in cell-cell recognition. Oligosaccharides are involved in many inflammatory processes and may also provide targets for tumor immunotherapy.

Glycoproteins are often linked to their oligosaccharides through asparagine (N) residues. These N-linked oligosaccharides are very diverse, but the many pathways by which they all form have a common first step. A 14 residue core oligosaccharide, containing two N-acetylglucosamine, nine mannose, and three glucose residues, is transferred from a dolichol phosphate donor molecule to certain N residues on the proteins (reviewed in Lehninger, A. L. et al. (1993) Principles of Biochemistry, Worth Publishers, New York, NY, pp. 931). Glycosylation is the most extensive of all post-translational modifications in proteins and is essential for the secretion, antigenicity, and clearance of glycoproteins.

A variety of enzymes which are involved in sugar metabolism participate directly or indirectly in glycosylation, such as certain pyrophosphorylases. ADP-glucose pyrophosphorylases play an important role in the biosynthesis of alpha 1,4-glucans (glycogen or starch) in bacteria and plants. Specifically, ADP-glucose pyrophosphorylases catalyze the synthesis of the activated glucosyl donor, ADP-glucose, from glucose-1-phosphate and ATP. ADP-glucose pyrophosphorylases are tetrameric, allosterically regulated enzymes. There are a number of conserved regions in the sequence of bacterial and plant ADP-glucose pyrophosphorylase subunits. Additionally, there are three regions which are considered signature patterns (ExPASy PROSITE database, documents PS00808-PS00810). The first two regions are N-terminal and have been proposed to be part of the allosteric and substrate-binding sites in the Escherichia coli enzyme. The third pattern corresponds to a conserved region in the central part of the enzymes.

In eukaryotic cells, mannose-1-phosphate guanyltransferase is involved in early steps of protein glycosylation. This enzyme participates in mannose metabolism, and its enzymatic products are channeled into glycoprotein synthesis. Mannose-1-phosphate guanyltransferase (MPG), also referred to as NDP-hexose pyrophosphorylase or GDP-mannose pyrophosphorylase B, catalyzes the conversion of GTP and α-D-mannose 1-phosphate into diphosphate and CDP-ethanolamine. This enzyme is very similar to CDP-glucose pyrophosphorylase and may be involved in the regulation of cell cycle progression. A cDNA coding for MPG1 was recently isolated from a Trichoderma reesei cDNA library (Kruszewska, J. S. et al. (1998) Curr. Genet. 33:445-500). The nucleotide sequence of the 1.6 kb cDNA revealed an ORF which encodes a protein of 364 amino acids. Sequence comparisons demonstrate that this protein shares 70% identity with the yeast Saccharomyces cerevisiae MPG1 gene and 75% identity with the Schizosaccharomyces pombe gene. MPGs are conserved among diverse organisms. For example, recent genome sequencing projects have identified MPG homologs in the plant Arabidopsis thaliana and the nematode Caenorhabditis elegans (SEQ ID NO:32 and SEQ ID NO:33, respectively).

Alterations in glycosylation are known to occur in a number of disorders and diseases such as carbohydrate-deficient glycoprotein syndromes (CDGSs). In the biochemical pathway upstream of MPG is an important enzyme called phosphomannomutase (PMM) which provides the mannose 1-phosphate required for the reaction catalyzed by MPG. PMM catalyzes the conversion of D-mannose 6-phosphate to D-mannose 1-phosphate and has been implicated in CDGSs. CDGSs are a group of hereditary multisystem disorders (Matthijs, G. et al. (1997) Nat. Genet. 16:88-92). The clinical phenotype of most CDGSs is dominated by severe psychomotor and mental retardation, as well as blood coagulation abnormalities as seen in thrombosis, bleeding,

or stroke-like episodes. The characteristic biochemical abnormality of CDGSs is the hypoglycosylation of glycoproteins. Depending on the type of CDGS, the carbohydrate side chains of glycoproteins are either truncated or completely missing from the protein core.

A new type of CDGS, designated as CDGS type 1B, has recently been described (Niehues, R. et al. (1998) Clin. Invest. 101:1414-1420). The clinical phenotype of this new disorder is fundamentally different from other types of CDGS in that no psychomotor or mental retardation is present. Instead, CDGS type 1B is a gastrointestinal disorder characterized by protein-losing enteropathy. Some patients who are affected with CDGS type 1B suffer from thrombosis and life-threatening bleeding. A deficiency of phosphomannose isomerase was identified as the most likely cause of this syndrome, and a therapy was developed in the form of oral administration of mannose (Niehues, supra). Mannose treatment can correct the clinical phenotype in CDGS type 1B. It is noteworthy that CDGS is the first inherited disorder in human metabolism that shows a decrease in available mannose. The above findings indicate that increasing blood mannose levels might correct some protein glycosylation deficiencies.

The discovery of new human transferase proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cancer, developmental disorders, gastrointestinal disorders, genetic disorders, immunological disorders, neurological disorders, reproductive disorders, and smooth muscle disorders.

SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, human transferase proteins, referred to collectively as "TRNSFS" and individually as "TRNSFS-1," "TRNSFS-2," "TRNSFS-3," "TRNSFS-4," "TRNSFS-5," "TRNSFS-6," "TRNSFS-7," "TRNSFS-8," "TRNSFS-9," "TRNSFS-10," "TRNSFS-11," "TRNSFS-12," "TRNSFS-13," "TRNSFS-14," and "TRNSFS-15." In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15 (SEQ ID NO:1-15), and fragments thereof.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-15 and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the

group consisting of SEQ ID NO:1-15 and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-15 and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-15 and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-15 and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30 (SEQ ID NO:16-30), and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:16-30 and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:16-30 and fragments thereof.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-15 and fragments thereof. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and

(b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-15 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from the group consisting of SEQ ID NO:1-15 and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of TRNSFS, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-15 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of TRNSFS, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-15 and fragments thereof.

BRIEF DESCRIPTION OF THE TABLES

Figures 1A and 1B show the amino acid sequence alignment between TRNSFS-1 (1632930; SEQ ID NO:1 and human myristoyl CoA:protein N-myristoyltransferase (GI 2443814; SEQ ID NO:31), produced using the multisequence alignment program of LASERGENE software (DNASTAR, Madison WI).

Figures 2A, 2B, 2C and 2D show the amino acid sequence alignments among TRNSFS-2 (2682663; SEQ ID NO:2), Arabidopsis thaliana MPG (GI 2642159; SEQ ID NO:32), and Caenorhabditis elegans MPG (GI 2804432; SEQ ID NO:33), produced using the multisequence alignment program of LASERGENE software (DNASTAR Inc, Madison WI).

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NO), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding TRNSFS.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods and algorithms used for identification of TRNSFS.

Table 3 shows useful fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was

cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding TRNSFS were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze TRNSFS, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"TRNSFS" refers to the amino acid sequences of substantially purified TRNSFS obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which, when bound to TRNSFS, increases or prolongs the duration of the effect of TRNSFS. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules which bind to and modulate the effect of TRNSFS.

An "allelic variant" is an alternative form of the gene encoding TRNSFS. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. Any given natural or recombinant gene may have none, one, or many allelic forms. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding TRNSFS include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as TRNSFS or a polypeptide with at least one functional characteristic of TRNSFS. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding TRNSFS, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding TRNSFS. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent TRNSFS. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of TRNSFS is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine, and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, "fragments," "immunogenic fragments," or "antigenic fragments" refer to fragments of TRNSFS which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or immunological activity of TRNSFS. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well

known in the art.

The term "antagonist" refers to a molecule which, when bound to TRNSFS, decreases the amount or the duration of the effect of the biological or immunological activity of TRNSFS. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of TRNSFS.

The term "antibody" refers to intact molecules as well as to fragments thereof, such as Fab, $F(ab')_2$, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind TRNSFS polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic TRNSFS, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that

total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acids strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding TRNSFS or fragments of TRNSFS may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of more than one Incyte Clone using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence encoding TRNSFS, by northern analysis is indicative of the presence of nucleic acids encoding TRNSFS in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding TRNSFS.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or Northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity" refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR, Madison WI) which creates alignments between two or more sequences according to methods selected by the user, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988) Gene 73:237-244.) Parameters for each method may be the default parameters provided by MEGALIGN or may be specified by the user. The clustal algorithm groups sequences into clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence B, into the sum of the residue matches between sequence A and sequence B, times one hundred. Gaps of low or of no similarity between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) Methods Enzymol. 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements

required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of TRNSFS. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of TRNSFS.

The phrases "nucleic acid" or "nucleic acid sequence," as used herein, refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those nucleic acid sequences which comprise a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:16-30, for example, as distinct from any other sequence in the same genome. For example, a fragment of SEQ ID NO:16-30 is useful in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:16-30 from related

polynucleotide sequences. A fragment of SEQ ID NO:16-30 is at least about 15-20 nucleotides in length. The precise length of the fragment of SEQ ID NO:16-30 and the region of SEQ ID NO:16-30 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment. In some cases, a fragment, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide.

The terms "operably associated" and "operably linked" refer to functionally related nucleic acid sequences. A promoter is operably associated or operably linked with a coding sequence if the promoter controls the translation of the encoded polypeptide. While operably associated or operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms "amplimer," "primer," "oligomer," and "probe," as these terms are commonly defined in the art.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding TRNSFS, or fragments thereof, or TRNSFS itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of TRNSFS polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with isoleucine). More rarely, a variant may have "nonconservative" changes (e.g., replacement of glycine with tryptophan). Analogous minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to TRNSFS. This definition may also include, for example, "allelic" (as defined above), "splice," "species," or "polymorphic" variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

THE INVENTION

The invention is based on the discovery of new human human transferase proteins (TRNSFS), the polynucleotides encoding TRNSFS, and the use of these compositions for the diagnosis, treatment, or prevention of cancer, developmental disorders, gastrointestinal disorders, genetic disorders, immunological disorders, neurological disorders, reproductive disorders, and smooth muscle disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding TRNSFS. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each TRNSFS were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The clones in column 5 were used to assemble the consensus nucleotide sequence of each TRNSFS and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods used to characterize each polypeptide through sequence homology and protein motifs. As shown in Figures 1A and 1B, SEQ ID NO:1 has chemical and

structural similarity with human myristoyl CoA:protein N-myristoyltransferase (GI 2443814; SEQ ID NO:31). In particular, SEQ ID NO:1 and human myristoyl CoA:protein N-myristoyltransferase share 74% identity, share two potential N-glycosylation sites, three potential casein kinase II phosphorylation sites, seven potential protein kinase C phosphorylation sites, the myristoyl CoA:protein N-myristoyltransferase signatures, and have similar isoelectric points, 7.7 and 8.2, respectively. SEQ ID NO:2 also has one potential bacterial hexapeptide-transferase signature from residue V_{256} to V_{284}. This signature is conserved among a number of bacterial transferases which are believed to belong to a single family and are involved in the biosynthesis of glycolipids, polysaccharides, and other macromolecules. As shown in Figures 2A, 2B, 2C and 2D, SEQ ID NO:2 has chemical and structural similarity with Arabidopsis thaliana MPG (GI 2642159; SEQ ID NO:32), and Caenorhabditis elegans MPG (GI 2804432; SEQ ID NO:33). In particular, SEQ ID NO:2 and Arabidopsis thaliana MPG share 61% identity, and MPGh and Caenorhabditis elegans MPG share 63% identity. Note that the ADP-glucose pyrophosphorylase signature of MPGh is also conserved within both, Arabidopsis thaliana and Caenorhabditis elegans MPGs. In addition, the potential N-glycosylation site at residue N_{322}, the potential casein kinase II phosphorylation sites at residues S_{78}, T_{136} and T_{191}, the potential tyrosine kinase phosphorylation site at residue Y_{144}, and the potential bacterial hexapeptide-transferase signature of SEQ ID NO:2 are conserved in both Arabidopsis thaliana and Caenorhabditis elegans MPGs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding TRNSFS. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:16-30 and to distinguish between SEQ ID NO:16-30 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express TRNSFS as a fraction of total tissues expressing TRNSFS. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing TRNSFS as a fraction of total tissues expressing TRNSFS. Column 5 lists the vectors used to subclone each cDNA library. Of particular note is the expression of SEQ ID NO:1 in reproductive, smooth muscle, and nervous tissue. Of particular note is the expression of SEQ ID NO:2 in reproductive and gastrointestinal tissue.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding TRNSFS were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the

cDNA libraries in column 2.

The invention also encompasses TRNSFS variants. A preferred TRNSFS variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the TRNSFS amino acid sequence, and which contains at least one functional or structural characteristic of TRNSFS.

The invention also encompasses polynucleotides which encode TRNSFS. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:16-30, which encodes TRNSFS.

The invention also encompasses a variant of a polynucleotide sequence encoding TRNSFS. In particular, such a variant polynucleotide sequence will have at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding TRNSFS. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:16-30 which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:16-30. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of TRNSFS.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding TRNSFS, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring TRNSFS, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode TRNSFS and its variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring TRNSFS under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding TRNSFS or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding TRNSFS and its derivatives without

altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode TRNSFS and TRNSFS derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding TRNSFS or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:16-30 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM

trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA), and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using the ABI 373 or 377 DNA sequencing systems (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding TRNSFS may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an

engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-306). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 primer analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode TRNSFS may be cloned in recombinant DNA molecules that direct expression of TRNSFS, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express TRNSFS.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter TRNSFS-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example,

oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding TRNSFS may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl. Acids Res. Symp. Ser. 7:215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 7:225-232.) Alternatively, TRNSFS itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of TRNSFS, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g, Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active TRNSFS, the nucleotide sequences encoding TRNSFS or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding TRNSFS. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding TRNSFS. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding TRNSFS and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results

Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding TRNSFS and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding TRNSFS. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus,TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding TRNSFS. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding TRNSFS can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding TRNSFS into the vector's multiple cloning site disrupts the *lac*Z gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of TRNSFS are needed, e.g. for the production of antibodies, vectors which direct high level expression of TRNSFS may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of TRNSFS. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel,

1995, supra; Grant et al. (1987) Methods Enzymol. 153:516-54; and Scorer, C. A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of TRNSFS. Transcription of sequences encoding TRNSFS may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding TRNSFS may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses TRNSFS in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of TRNSFS in cell lines is preferred. For example, sequences encoding TRNSFS can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These

include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* or *apr*˙ cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* or *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding TRNSFS is inserted within a marker gene sequence, transformed cells containing sequences encoding TRNSFS can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding TRNSFS under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding TRNSFS and that express TRNSFS may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of TRNSFS using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on TRNSFS is preferred, but a competitive binding assay may be employed. These and other assays are well known in the

art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St Paul MN, Sect. IV; Coligan, J. E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding TRNSFS include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding TRNSFS, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding TRNSFS may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode TRNSFS may be designed to contain signal sequences which direct secretion of TRNSFS through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas, VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding TRNSFS may be ligated to a heterologous sequence resulting in translation of

a fusion protein in any of the aforementioned host systems. For example, a chimeric TRNSFS protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of TRNSFS activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the TRNSFS encoding sequence and the heterologous protein sequence, so that TRNSFS may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled TRNSFS may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, preferably ^{35}S-methionine.

Fragments of TRNSFS may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of TRNSFS may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of TRNSFS and human transferase proteins. In addition, the expression of TRNSFS is closely associated with cancerous and proliferating, gastrointestinal, inflamed, immunological, nervous, reproductive and smooth muscle tissue and fetal cell lines. Therefore, TRNSFS appears to play a role in cancer, developmental disorders, gastrointestinal disorders,

genetic disorders, immunological disorders, neurological disorders, reproductive disorders, and smooth muscle disorders. In the treatment of disorders associated with increased TRNSFS expression or activity, it is desirable to decrease the expression or activity of TRNSFS. In the treatment of disorders associated with decreased TRNSFS expression or activity, it is desirable to increase the expression or activity of TRNSFS.

Therefore, in one embodiment, TRNSFS or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of TRNSFS. Examples of such disorders include, but are not limited to, a cancer, such as adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; a developmental disorder, such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy, spina bifida, anencephaly, craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing loss; a gastrointestinal disorder, such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, and acquired immunodeficiency syndrome (AIDS) enteropathy; a genetic disorder, such as Lesch-Nyhan syndrome, mitochondrial carnitine palmitoyl transferase deficiency, carnitine deficiency, peroxisomal acyl-CoA oxidase deficiency, peroxisomal thiolase deficiency, peroxisomal bifunctional protein deficiency, mitochondrial very-long-chain acyl-CoA dehydrogenase deficiency, mitochondrial medium-chain acyl-CoA dehydrogenase deficiency, mitochondrial short-chain acyl-CoA dehydrogenase deficiency, mitochondrial electron transport flavoprotein and

electron transport flavoprotein:ubiquinone oxidoreductase deficiency, mitochondrial trifunctional protein deficiency, mitochondrial short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, adrenoleukodystrophy, Alport's syndrome, choroideremia, Duchenne and Becker muscular dystrophy, Down's syndrome, cystic fibrosis, chronic granulomatous disease, Gaucher's disease, Huntington's chorea, Marfan's syndrome, muscular dystrophy, myotonic dystrophy, pycnodysostosis, Refsum's syndrome, retinoblastoma, sickle cell anemia, thalassemia, Werner syndrome, von Willebrand's disease, Wilms' tumor, and Zellweger syndrome; an immunological disorder, such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a neurological disorder, such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease; prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome; fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorder of the central nervous system, cerebral palsy, a neuroskeletal disorder, an autonomic nervous system disorder, a cranial nerve disorder, a spinal cord disease, muscular dystrophy and other neuromuscular

disorder, a peripheral nervous system disorder, dermatomyositis and polymyositis; inherited, metabolic, endocrine, and toxic myopathy; myasthenia gravis, periodic paralysis; a mental disorder including mood, anxiety, and schizophrenic disorders; seasonal affective disorder (SAD); akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; a reproductive disorder, such as disorders of prolactin production; infertility, including tubal disease, ovulatory defects, and endometriosis, disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea, disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; and a smooth muscle disorder, such as angina, anaphylactic shock, arrhythmias, asthma, cardiovascular shock, Cushing's syndrome, hypertension, hypoglycemia, myocardial infarction, migraine, and pheochromocytoma, and myopathies including cardiomyopathy, encephalopathy, epilepsy, Kearns-Sayre syndrome, lactic acidosis, myoclonic disorder, and ophthalmoplegia. A smooth muscle disorder is defined as any impairment or alteration in the normal action of smooth muscle and may include those disorders listed above. Smooth muscle includes, but is not limited to, that of the blood vessels, gastrointestinal tract, heart, and uterus.

In another embodiment, a vector capable of expressing TRNSFS or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of TRNSFS including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified TRNSFS in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of TRNSFS including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of TRNSFS may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of TRNSFS including, but not limited to, those listed above.

In a further embodiment, an antagonist of TRNSFS may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of TRNSFS. Examples of such disorders include, but are not limited to, those described above. In one aspect, an antibody which specifically binds TRNSFS may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express

TRNSFS.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding TRNSFS may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of TRNSFS including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of TRNSFS may be produced using methods which are generally known in the art. In particular, purified TRNSFS may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind TRNSFS. Antibodies to TRNSFS may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with TRNSFS or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to TRNSFS have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of TRNSFS amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to TRNSFS may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce TRNSFS-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. 86: 3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for TRNSFS may also be generated. For example, such fragments include, but are not limited to, F(ab')2 fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between TRNSFS and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering TRNSFS epitopes is preferred, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for TRNSFS. Affinity is expressed as

an association constant, K_a, which is defined as the molar concentration of TRNSFS-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple TRNSFS epitopes, represents the average affinity, or avidity, of the antibodies for TRNSFS. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular TRNSFS epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the TRNSFS-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of TRNSFS, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of TRNSFS-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding TRNSFS, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding TRNSFS may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding TRNSFS. Thus, complementary molecules or fragments may be used to modulate TRNSFS activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding TRNSFS.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the

polynucleotides encoding TRNSFS. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding TRNSFS can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding TRNSFS. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding TRNSFS. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding TRNSFS.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These

include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding TRNSFS. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of TRNSFS, antibodies to TRNSFS, and mimetics, agonists, antagonists, or inhibitors of TRNSFS. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial,

intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution,

Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of TRNSFS, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example TRNSFS or fragments thereof, antibodies of TRNSFS, and agonists, antagonists or inhibitors of

TRNSFS, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind TRNSFS may be used for the diagnosis of disorders characterized by expression of TRNSFS, or in assays to monitor patients being treated with TRNSFS or agonists, antagonists, or inhibitors of TRNSFS. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for TRNSFS include methods which utilize the antibody and a label to detect TRNSFS in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring TRNSFS, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of TRNSFS expression. Normal or standard values for TRNSFS expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to TRNSFS under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of TRNSFS expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding TRNSFS may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of TRNSFS may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of TRNSFS, and to monitor regulation of TRNSFS levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding TRNSFS or closely related molecules may be used to identify nucleic acid sequences which encode TRNSFS. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding TRNSFS, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the TRNSFS encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:16-30 or from genomic sequences including promoters, enhancers, and introns of the TRNSFS gene.

Means for producing specific hybridization probes for DNAs encoding TRNSFS include the cloning of polynucleotide sequences encoding TRNSFS or TRNSFS derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S, or by

enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding TRNSFS may be used for the diagnosis of disorders associated with expression of TRNSFS. Examples of such disorders include, but are not limited to, a cancer, such as adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; a developmental disorder, such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy, spina bifida, anencephaly, craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing loss; a gastrointestinal disorder, such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, and acquired immunodeficiency syndrome (AIDS) enteropathy; a genetic disorder, such as Lesch-Nyhan syndrome, mitochondrial carnitine palmitoyl transferase deficiency, carnitine deficiency, peroxisomal acyl-CoA oxidase deficiency, peroxisomal thiolase deficiency, peroxisomal bifunctional protein deficiency, mitochondrial very-long-chain acyl-CoA dehydrogenase deficiency, mitochondrial medium-chain acyl-CoA dehydrogenase deficiency, mitochondrial short-chain acyl-CoA dehydrogenase deficiency, mitochondrial electron transport flavoprotein and electron transport flavoprotein:ubiquinone oxidoreductase deficiency, mitochondrial trifunctional protein deficiency, mitochondrial short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, adrenoleukodystrophy, Alport's syndrome, choroideremia, Duchenne and Becker muscular dystrophy, Down's syndrome, cystic fibrosis, chronic granulomatous disease, Gaucher's disease,

Huntington's chorea, Marfan's syndrome, muscular dystrophy, myotonic dystrophy, pycnodysostosis, Refsum's syndrome, retinoblastoma, sickle cell anemia, thalassemia, Werner syndrome, von Willebrand's disease, Wilms' tumor, and Zellweger syndrome; an immunological disorder, such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a neurological disorder, such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease; prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome; fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorder of the central nervous system, cerebral palsy, a neuroskeletal disorder, an autonomic nervous system disorder, a cranial nerve disorder, a spinal cord disease, muscular dystrophy and other neuromuscular disorder, a peripheral nervous system disorder, dermatomyositis and polymyositis; inherited, metabolic, endocrine, and toxic myopathy; myasthenia gravis, periodic paralysis; a mental disorder including mood, anxiety, and schizophrenic disorders; seasonal affective disorder (SAD); akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid

psychoses, postherpetic neuralgia, and Tourette's disorder; a reproductive disorder, such as disorders of prolactin production; infertility, including tubal disease, ovulatory defects, and endometriosis, disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea, disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; and a smooth muscle disorder, such as angina, anaphylactic shock, arrhythmias, asthma, cardiovascular shock, Cushing's syndrome, hypertension, hypoglycemia, myocardial infarction, migraine, and pheochromocytoma, and myopathies including cardiomyopathy, encephalopathy, epilepsy, Kearns-Sayre syndrome, lactic acidosis, myoclonic disorder, and ophthalmoplegia. The polynucleotide sequences encoding TRNSFS may be used in Southern or Northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered TRNSFS expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding TRNSFS may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding TRNSFS may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding TRNSFS in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of TRNSFS, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding TRNSFS, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with

values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding TRNSFS may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding TRNSFS, or a fragment of a polynucleotide complementary to the polynucleotide encoding TRNSFS, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantitation of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of TRNSFS include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See,

e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding TRNSFS may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding TRNSFS on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, TRNSFS, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a

variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between TRNSFS and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with TRNSFS, or fragments thereof, and washed. Bound TRNSFS is then detected by methods well known in the art. Purified TRNSFS can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding TRNSFS specifically compete with a test compound for binding TRNSFS. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with TRNSFS.

In additional embodiments, the nucleotide sequences which encode TRNSFS may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. [Attorney Docket No: PF-0592 P, filed September 10, 1998], U.S. Ser. No. [Attorney Docket No: PF-0624 P, filed November 4, 1998], and U.S. Ser. No. 60/133,642, are hereby expressly incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated

from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8, QIAWELL 8 Plus, QIAWELL 8 Ultra plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified

fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing systems (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian,

vertebrate, and eukaryote databases, and BLOCKS to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Str. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:16-30. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\%\ \text{sequence identity} \times \%\ \text{maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding TRNSFS occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular,

dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation/trauma, cell proliferation, fetal, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Extension of TRNSFS Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:16 and of SEQ ID NO:18-30 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+}, $(NH_4)_2SO_4$, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 μl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μl to 10 μl aliquot of the reaction mixture

was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:16 and of SEQ ID NO:18-30 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

The full length nucleic acid sequence of SEQ ID NO: 17 was produced by extension of an appropriate fragment of the full length molecule, using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate extension of an antisense polynucleotide, and the other was synthesized to initiate extension of a sense polynucleotide. Primers were used to facilitate the extension of the known sequence "outward" generating amplicons containing new unknown nucleotide sequence for the region of interest. The initial primers were designed from the cDNA using OLIGO 4.06 software (National Biosciences, Plymouth, MN), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer

dimerizations was avoided.

Selected human cDNA libraries (Life Technologies) were used to extend the sequence. If more than one extension is necessary or desired, additional sets of primers are designed to further extend the known region.

High fidelity amplification was obtained by following the instructions for the XL-PCR kit (Perkin-Elmer Corp., Norwalk, CT) and thoroughly mixing the enzyme and reaction mix. PCR was performed using the PTC-200 thermal cycler (MJ Research, Inc., Watertown, MA), beginning with 40 pmol of each primer and the recommended concentrations of all other components of the kit, with the following parameters:

Step 1	94° C for 1 min (initial denaturation)
Step 2	65° C for 1 min
Step 3	68° C for 6 min
Step 4	94° C for 15 sec
Step 5	65° C for 1 min
Step 6	68° C for 7 min
Step 7	Repeat steps 4 through 6 for an additional 15 cycles
Step 8	94° C for 15 sec
Step 9	65° C for 1 min
Step 10	68° C for 7:15 min
Step 11	Repeat steps 8 through 10 for an additional 12 cycles
Step 12	72° C for 8 min
Step 13	4° C (and holding)

A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a low concentration (about 0.6% to 0.8%) agarose mini-gel to determine which reactions were successful in extending the sequence. Bands thought to contain the largest products were excised from the gel, purified using QIAQUICK DNA gel purification kit (Qiagen, Inc.), and trimmed of overhangs using Klenow enzyme to facilitate religation and cloning.

After ethanol precipitation, the products were redissolved in 13 μl of ligation buffer, 1μl T4-DNA ligase (15 units) and 1μl T4 polynucleotide kinase were added, and the mixture was incubated at room temperature for 2 to 3 hours, or overnight at 16° C. Competent E. coli cells (in 40 μl of appropriate media) were transformed with 3 μl of ligation mixture and cultured in 80 μl of SOC medium. (See, e.g., Sambrook, supra, Appendix A, p. 2.) After incubation for one hour at 37°C, the E. coli mixture was plated on Luria Bertani (LB) agar (See, e.g., Sambrook, supra, Appendix A, p. 1) containing carbenicillin (2x carb). The following day, several colonies were randomly picked from each plate and cultured in 150 μl of liquid LB/2x carb medium placed in an individual well of an appropriate commercially-available sterile 96-well microtiter plate. The following day, 5 μl of each overnight culture was transferred into a non-sterile 96-well plate and, after dilution 1:10 with water, 5 μl from each sample was transferred into a PCR array.

For PCR amplification, 18 μl of concentrated PCR reaction mix (3.3x) containing 4 units of rTth DNA polymerase, a vector primer, and one or both of the gene specific primers used for the extension reaction were added to each well. Amplification was performed using the following conditions:

Step 1	94° C for 60 sec
Step 2	94° C for 20 sec
Step 3	55° C for 30 sec
Step 4	72° C for 90 sec
Step 5	Repeat steps 2 through 4 for an additional 29 cycles
Step 6	72° C for 180 sec
Step 7	4° C (and holding)

Aliquots of the PCR reactions were run on agarose gels together with molecular weight markers. The sizes of the PCR products were compared to the original partial cDNAs, and appropriate clones were selected, ligated into plasmid, and sequenced.

In like manner, the nucleotide sequence of SEQ ID NO:17 is used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for 5' extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:16-30 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-^{32}P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba1, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography and compared.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array

elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

VIII. Complementary Polynucleotides

Sequences complementary to the TRNSFS-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring TRNSFS. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of TRNSFS. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the TRNSFS-encoding transcript.

IX. Expression of TRNSFS

Expression and purification of TRNSFS is achieved using bacterial or virus-based expression systems. For expression of TRNSFS in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac*

operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express TRNSFS upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of TRNSFS in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding TRNSFS by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, TRNSFS is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from TRNSFS at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified TRNSFS obtained by these methods can be used directly in the following activity assay.

X. Demonstration of TRNSFS Activity

TRNSFS activity is determined by measuring the transfer of a radiolabeled molecular group from a donor to an acceptor molecule in the presence of TRNSFS. For example, HNK sulfotransferase activity is determined in a reaction mixture that contains 0.02 mM [^{35}S]PAPS, 25 μl of IgG bead-bound enzyme suspension, 0.1 mM acceptor oligosaccharides or 0.0265 mM acceptor glycolipids in 100 mM TRIS-HCl, pH 7.2, 0.1% Triton X-100, 10 mM $MnCl_2$, and 2.5 mM ATP. The mixture is incubated for two hours at 37°C. The reaction products are adjusted to 0.25 M ammonium formate, pH 4.0, and separated on a C18 reverse phase chromatography column. The column is washed and the products are eluted with 70% methanol. The radioactivity recovered in the acceptor molecule is measured using a liquid scintillation counter and is

proportional to the activity of HNK sulfotransferase in the assay.

Alternatively, myristoyl CoA:protein N-myristoyltransferase activity is demonstrated as the ability of TRNSFS to myristoylate a synthetic peptide substrate using the methods known in the art. (Giang, D.K. and Cravatt, B.F. (1998) J. Biol. Chem. 273:6595-6598; and Towler and Glaser (1986) Proc. Natl. Acad. Sci., 83:2812-2816.) [^{3}H]Myristoyl-CoA (0.75 μCi; 52 Ci/mmol; 0.3 μM; Amersham Pharmacia Biotech) is added to a mixture of COS-7 total cell protein (7.5 μg) and peptide substrate (200 μM; Towler and Glaser, supra) in a reaction buffer of 30 mM tris-HCl, pH 7.5, with 0.5 mM EDTA, 0.5 mM EGTA, 1.0% (v/v) Triton X-100, and 4.5 mM β-mercaptoethanol (total reaction volume of 50 μl). The reaction is allowed to proceed for 10 min at 25 °C, then quenched with 50 μl of methanol followed by 5 μl of 100% trichloroacetic acid, placed on ice for 10 min, and spun at 10,000 x g for 5 min. Aliquots (25 μl) of the supernatant are analyzed by reverse-phase high pressure liquid chromatography. A myristoylated peptide is synthesized as described (Towler and Glaser, supra) and used as a standard to define the elution times for myristoylated peptide products. Column fractions (1 ml) are collected and counted by scintillation counting. In all cases, control reactions without peptide are also analyzed and subtracted from reactions with peptide to provide myristoyl-transferase reaction rates. Initial rates are determined from reactions in which less than 20% myristoylated product is formed. Myristoyltransferase reaction rate is proportional to the amount of TRNSFS present in the sample.

Alternatively, mannose-1-phosphate guanyltransferase activity is determined by combining TRNSFS with its substrates GTP and α-D-mannose-1-phosphate at stoichometric quantities under buffered conditions. At appropriate time points the products, CDP-ethanolamine and diphosphate are measured with chromatographic methods, whereby the reaction products are separated from the substrates. Under the standardized conditions of the assay, the amounts of CDP-ethanolamine and diphosphate produced are directly proportional to the activity of TRNSFS in biological samples.

XI. Functional Assays

TRNSFS function is assessed by expressing the sequences encoding TRNSFS at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression

of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of TRNSFS on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding TRNSFS and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding TRNSFS and other genes of interest can be analyzed by Northern analysis or microarray techniques.

XII. Production of TRNSFS Specific Antibodies

TRNSFS substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the TRNSFS amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase

immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring TRNSFS Using Specific Antibodies

Naturally occurring or recombinant TRNSFS is substantially purified by immunoaffinity chromatography using antibodies specific for TRNSFS. An immunoaffinity column is constructed by covalently coupling anti-TRNSFS antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing TRNSFS are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of TRNSFS (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/TRNSFS binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and TRNSFS is collected.

XIV. Identification of Molecules Which Interact with TRNSFS

TRNSFS, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent. (See, e.g., Bolton et al. (1973) Biochem. J. 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled TRNSFS, washed, and any wells with labeled TRNSFS complex are assayed. Data obtained using different concentrations of TRNSFS are used to calculate values for the number, affinity, and association of TRNSFS with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

TABLE 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	16	1632930	COLNNOT19	1632930H1, 1632930T6.comp, and 1632930F6 (COLNNOT19), 2616972T6.comp (GBLANOT01),1001793H1 (BRSTNOT03), 1322727H1 (BLADNOT04), 2535979H1 (BRAINOT18), 2779012T6.comp (OVARTUT03)
2	17	2682663	SINIUCT01	2682663H1 (SINIUCT01), 2483825H1 (SMCANOT01), 785487R1 (PROSNOT05), 2643432F6 (LUNGTUT08), 1214388H1 (BRSTTUT01), 2122443T6 (BRSTNOT07), 2278985R6 (PROSNON01)
3	18	1265094	SYNORAT05	266269H1 (HNT2NOT01), 605479R6 and 605479T6 (BRSTTUT01), 870033R6 (LUNGAST01), 928166R6 (BRAINOT04), 1265094H1 (SYNORAT05), 1914656H1 (PROSTUT04), 2737452H1 (OVARNOT09), 3351376H1 (PROSNOT28), 4998035H1 (MYEPTXT02), 5121429H1 (SMCBUNT01)
4	19	1404963	LATRTUT02	1404963H1 and 1404963T6 (LATRTUT02), 1742179T6 (HIPONON01), 2055278X19R1 (BEPINOT01), SBMA02021F1, SBMA03096F1, SBMA01345F1
5	20	1405058	LATRTUT02	154037H1 (THP1PLB02), 1405058F6, 1405058H1, and 1405058T6 (LATRTUT02), 2371445F6 (ADRENOT07), 3235888F7 (COLNUCT03), 3674493H1 (PLACNOT07), 4985152H1 (LIVRTUT10)
6	21	1420940	KIDNNOT09	493640X19 (HNT2NOT01), 983695H1 (TONGTUT01), 1361219F6, 1361219X11, 1361219X13, and 1362434X11 (LUNGNOT12), 1420940H1 (KIDNNOT09), 1499443T6 (SINTBST01), 3655410F6 (ENDINOT02)
7	22	1784742	BRAINOT10	1286822H1 (BRAINOT11), 1784742H1 (BRAINOT10), 3243626H1 and 3244456F6 (BRAINOT19), 5013854F6 (BRAXNOT03)
8	23	1967138	BRSTNOT04	1513726T6 (PANCTUT01), 1967138H1 (BRSTNOT04), SAEA03142R1, SAEA01673F1
9	24	2124351	BRSTNOT07	288743F1 (EOSIHET02), 582937H1 (PROSNOT02), 890499R1 (STOMTUT01), 1380837F1 (BRAITUT08), 1444442F1 (THYRNOT03), 2124351H1 (BRSTNOT07), 2159702F6 (ENDCNOT02)
10	25	2153162	BRAINOT09	269898X29R1, 495807F1 and 495807R1 (HNT2NOT01), 1450490F1 (PENITUT01), 2153162H1, 2153162X14F1, 2153162X22F1, 2153162X40F1, and 2153162X46F1 (BRAINOT09), 3114632H1 (BRSTNOT17)
11	26	2617407	GBLANOT01	2039925T6 (HIPONON02), 2617407F6 and 2617407H1 (GBLANOT01), 2620445R6 (KERANOT02), SBGA01193F1, SBGA05513F1, SBGA02306F1, SBGA03105F1
12	27	2963717	SCORNOT04	1627889X24F1 (COLNPOT01), 2963717H1 and 2963717T6 (SCORNOT04), SBZA04180V1, SBZA00122V1, SBZA04721V1, SBZA00694V1
13	28	3360857	PROSTUT16	538662R6 (LNODNOT02), 830729R1 and 830729T1 (PROSTUT04), 3360857H1 (PROSTUT16), 5069726H1 (PANCNOT23)

TABLE 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
14	29	3449671	UTRSNON03	1418639T1 (KIDNNOT09), 1626239F6 (COLNPOT01), 1726392T6 (PROSNOT14), 2643253F6 (LUNGTUT08), 3049827F6 (LUNGNOT25), 3449671H1 (UTRSNON03), SBHA03052F1, SBHA03662F1, SBHA02654F1
15	30	5497787	BRABDIR01	358882R6 (SYNORAB01), 773882R6 (COLNNOT05), 5497787H1 (BRABDIR01), 5673443H1 (293TF2T01)

TABLE 2

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequences	Analytical Methods
1	498	T64 S68 S166 S350 T462 T488 S220 S240 S258 T270 T295 T325 S350 S417 S490	N319 N460	Myristoyl-CoA protein N-myristoyltransferase: E246 – K254 K468 – G474 Myristoyl-CoA protein N-myristoyltransferase: E150 – I228 S240 – A285 G286 – F362 L436 – T488	Myristoyl CoA:protein N-myristoyltransferase (g2443814) [Homo sapiens]	BLAST, Motifs, BLOCKS
2	360	T290 S78 T136 T191 S301 S348 S352 T21 T153 S168 S235 S259 Y144	N265 N271 N322	Bacterial hexapeptide-transferase: V256 – V284 Putative ADP-glucose pyrophosphorylase: V7 – A44 V106 – Y144	Mannose-1-phosphate guanyltransferase (g2642159) [Arabidopsis thaliana] Mannose-1-phosphate guanyltransferase (g2804432) [Caenorhabditis elegans]	BLAST, Motifs, BLOCKS
3	519	S403 T248 T349 S409 S508 S18 T452	N408	TPR Domains: Y171 - P199 L205 - P223 W273 - P301	O-linked GlcNAc transferase [Methanobacterium thermoautotrophicum] (g2621120)	BLAST, PFAM, Motifs
4	225	S176 S4 S117 S155 S96 S101 S111 T146 T149 T175	N91	Purine/pyrimidine phosphoribosyl-transferase Domain: Y35 - V225	hypoxanthine (guanine) phosphoribosyl-transferase (g461344)	BLAST, PFAM, BLOCKS, Motifs
5	338	T103 T120 S239 T18 S41 T312	N232	Transmembrane Domain: G177 - A202	octaprenyltransferase (g4982095)	BLAST, HMM, Motifs
6	619	S92 T176 S180 T198 T250 T285 S308 T313 T394 T453 T527 T548 T430 Y439	N195 N298	ATP/GTP-binding site (P-loop): G49 - T56	ATP sulfurylase/APS kinase 2 [Homo sapiens] (g3342266)	BLAST, Motifs
7	284	S4 T11 T157 S174 T205 S260 S104 S148 S153 Y172		Sulfotransferase Protein Domain: H23 - K272	Sulfotransferase-like protein (g1173670)	BLAST, PFAM, Motifs, BLOCKS

TABLE 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous Sequences	Analytical Methods
8	205	S49 T45 S201		Transmembrane Domain: L105 - L124 L169 - Y185	phosphatidylethanol-amine N-methyl-transferase [Rattus norvegicus] (g310195)	BLAST, HMM, Motifs
9	414	T88 T239 S64 S96 S107 S257 S287 T344 S374 S375 S100 T312 S367	N134 N209 N280 N370	Signal Peptide: M1 - A31 Transmembrane Domain: L9 - D27	HNK-1 sulfotransferase [Rattus norvegicus] (g2660716)	BLAST, SPScan, HMM, Motifs
10	660	S20 S93 T118 S153 T176 S233 S247 S248 S270 S280 T285 T433 S550 T24 T61 S105 T188 S362 S535 S632 Y104		Transmembrane Domain: T41 - I58	N-acetylglucosaminyl-transferase I [Mus musculus] (g193527)	BLAST, HMM, Motifs
11	386	S121 S107 T217 S252 S364 T380 S35 S50 T81 T287 Y243	N30 N308 N329	Transmembrane Domain: M7 - F23	N-acetylglucosamine 6-O-sulfotransferase (g4927116) [Mus musculus]	BLAST, HMM, Motifs
12	803	S739 S178 S195 T425 S471 T740 S775 T799 S38 S158 T182 S189 T313 S354 S396 T601 S734 S735 S744	N312	Acyltransferases ChoActase/COT/CPT family: S170 - A759	carnitine palmitoyltransferase I [Rattus norvegicus] (g294521)	BLAST, PFAM, Motifs, BLOCKS, ProfileScan
13	295	T68 T83 S252 S88			glycine N-methyltransferase [Sus scrofa] (g217690)	BLAST, Motifs
14	575	S350 S40 S57 S210 T233 S273 S305 T494 T2 S3 S44 T284 T345 S371 S549	N110 N247 N250	Transmembrane Domain: T73 - R94	putative 3,4-dihydroxy-2-butanone kinase [Lycopersicon esculentum] (g1929056)	BLAST, HMM, Motifs
15	180	T15			O-GlcNAc transferase p110 subunit (g1931579)	BLAST, Motifs

TABLE 3

Nucleotide SEQ ID NO:	Useful Fragments of Nucleotide Sequence	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Fraction of Total)	Vector
16	170 -214	Reproductive Nervous Smooth Muscle	Cancer Inflammation	pINCY
17	377 - 406	Reproductive Gastrointestinal	Cancer (0.530) Inflammation (0.280)	pINCY
18	711 - 770, 915 - 959 1503 - 1562	Reproductive (0.346) Nervous (0.212)	Cancer (0.519) Inflammation (0.173)	PSPORT1
19	649 - 693	Nervous (0.368) Cardiovascular (0.263) Gastrointestinal (0.105) Reproductive (0.105) Hematopoietic/Immune (0.105)	Cancer (0.789) Inflammation (0.105)	pINCY
20	833 - 892	Gastrointestinal (0.238) Hematopoietic/Immune (0.190) Cardiovascular (0.143)	Inflammation (0.429) Cancer (0.381) Cell proliferation (0.238)	pINCY
21	942 - 986	Cardiovascular (0.245)Gastrointestinal (0.170) Reproductive (0.170) Endocrine (0.151)	Cancer (0.396) Inflammation (0.302) Cell Proliferation (0.170)	pINCY
22	2 - 97	Nervous (0.882) Endocrine (0.059) Developmental (0.059)	Neurological (0.294) Inflammation (0.235) Cancer (0.176)	pINCY
23	3 - 62	Reproductive (0.390) Nervous (0.186) Gastrointestinal (0.119) Cardiovascular (0.119)	Cancer (0.559) Trauma (0.136) Inflammation (0.102)	PSPORT1
24	396 - 440 444 - 503	Reproductive (0.286) Nervous (0.265) Musculoskeletal (0.122) Hematopoietic/Immune (0.102)	Cancer (0.551) Inflammation (0.245) Cell proliferation (0.143)	pINCY
25	207 - 266 321 - 380	Reproductive (0.218) Nervous (0.188) Gastrointestinal (0.139)	Cancer (0.545) Inflammation (0.168)	pINCY
26	264 - 323 1272 - 1331	Dermatologic (0.500) Gastrointestinal (0.500)	Inflammation (0.500) Cell proliferation (0.500)	pINCY
27	310 - 370 505 - 547	Nervous (0.600) Gastrointestinal (0.133) Musculoskeletal (0.133) Reproductive (0.133)	Cancer (0.333) Trauma (0.200) Inflammation (0.133)Neurological (0.133)	pINCY
28	368 - 412	Gastrointestinal (0.417) Reproductive (0.417) Hematopoietic/Immune (0.167)	Cancer (0.333) Trauma (0.333) Inflammation (0.250)	pINCY
29	458 – 502, 1196 - 1381 1460 - 1513	Reproductive (0.279) Gastrointestinal (0.197) Nervous (0.131)	Cancer (0.492) Inflammation (0.164) Cell proliferation (0.164)	pINCY
30	236 - 280	Gastrointestinal (0.375) Endocrine (0.125) Hematopoietic/Immune (0.125) Musculoskeletal (0.125) Nervous (0.125)	Cancer (0.375) Inflammation (0.375) Neurological (0.125)	pINCY

TABLE 4

Polynucleotide SEQ ID NO:	Library	Library Description
16	COLNNOT19	The library was constructed using RNA isolated from the cecal tissue of an 18-year-old Caucasian female. The cecal tissue, along with the appendix and ileum tissues, were removed during bowel anastomosis. Pathology indicated Crohn's disease of the ileum, involving 15 cm of the small bowel.
17	SINIUCT01	The library ws constructed using RNA isolated from ileum tissue removed from a 420year-old Caucasian male during a total intra-abdominal colectomy and endoscopic jejunostomy. Pathology indicated that the disease was most severe in the colon with the distal end completely ulcerated. Patient history included tobacco abuse. Previous surgeries included polypectomy, colonoscopy, and spinal canal exploration. Family history included benign hypertension, cerebrovascular disease, athersclerotic coronary artery disease, and type II diabetes.
18	SYNORAT05	The library was constructed using RNA isolated from the knee synovial tissue of a 62-year-old female with rheumatoid arthritis.
19	LATRTUT02	The library was constructed using RNA isolated from a myxoma removed from the left atrium of a 43-year-old Caucasian male during annuloplasty. Pathology indicated atrial myxoma. Patient history included pulmonary insufficiency, acute myocardial infarction, atherosclerotic coronary artery disease, hyperlipidemia, and tobacco use. Family history included benign hypertension, acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
20	LATRTUT02	The library was constructed using RNA isolated from a myxoma removed from the left atrium of a 43-year-old Caucasian male during annuloplasty. Pathology indicated atrial myxoma. Patient history included pulmonary insufficiency, acute myocardial infarction, atherosclerotic coronary artery disease, hyperlipidemia, and tobacco use. Family history included benign hypertension, acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
21	KIDNNOT09	The library was constructed using RNA isolated from the kidney tissue of a Caucasian male fetus, who died at 23 weeks' gestation.
22	BRAINOT10	The library was constructed using RNA isolated from diseased cerebellum tissue removed from the brain of a 74-year-old Caucasian male, who died from Alzheimer's disease.
23	BRSTNOT04	The library was constructed using RNA isolated from breast tissue removed from a 62-year-old East Indian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated an invasive grade 3 ductal carcinoma. Patient history included benign hypertension, hyperlipidemia, and hematuria. Family history included cerebrovascular and cardiovascular disease, hyperlipidemia, and liver cancer.
24	BRSTNOT07	The library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.
25	BRAINOT09	The library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus, who died at 23 weeks' gestation.

TABLE 4 (cont.)

Polynucleotide SEQ ID NO:	Library	Library Description
26	GBLANOT01	The library was constructed using RNA isolated from diseased gallbladder tissue removed from a 53-year-old Caucasian female during a cholecystectomy. Pathology indicated mild chronic cholecystitis and cholelithiasis with approximately 150 mixed gallstones. Family history included benign hypertension.
27	SCORNOT04	The library was constructed using RNA isolated from cervical spinal cord tissue removed from a 32-year-old Caucasian male who died from acute pulmonary edema and bronchopneumonia, bilateral pleural and pericardial effusions, and malignant lymphoma (natural killer cell type). Patient history included probable cytomegalovirus infection, hepatic congestion and steatosis, splenomegaly, hemorrhagic cystitis, thyroid hemorrhage, and Bell's palsy. Surgeries included colonoscopy, large intestine biopsy, adenotonsillectomy, and nasopharyngeal endoscopy and biopsy; treatment included radiation therapy.
28	PROSTUT16	The library was constructed using RNA isolated from prostate tumor tissue removed from a 55-year-old Caucasian male. Pathology indicated adenocarcinoma, Gleason grade 5+4. Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Patient history included calculus of the kidney. Family history included lung cancer and breast cancer.
29	UTRSNON03	The normalized library was constructed from 6.4 million independent clones from a uterus library. RNA was isolated from uterine myometrial tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Pathology for the associated tumor tissue indicated uterine leiomyoma. Patient history included ventral hernia and a benign ovarian neoplasm. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9928).
30	BRABDIR01	The library was constructed using RNA isolated from diseased cerebellum tissue removed from the brain of a 57-year-old Caucasian male, who died from a cerebrovascular accident. Patient history included Huntington's disease, emphysema, and tobacco abuse.

TABLE 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	*ESTs:* Probability value= 1.0E-8 or less *Full Length sequences*: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	*ESTs:* fasta E value=1.06E-6 *Assembled ESTs*: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less *Full Length sequences:* fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS and PRINTS databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and Probability value= 1.0E-3 or less
PFAM	A Hidden Markov Models-based application useful for protein family search.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits, depending on individual protein families

TABLE 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Score= 4.0 or greater
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. supra; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, and fragments thereof.

2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.

3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.

4. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 3.

5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.

6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.

7. A method for detecting a polynucleotide, the method comprising the steps of:

(a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and

(b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.

8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.

9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, and

fragments thereof.

10. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 9.

11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.

12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.

13. A host cell comprising the expression vector of claim 12.

14. A method for producing a polypeptide, the method comprising the steps of:

a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and

b) recovering the polypeptide from the host cell culture.

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

16. A purified antibody which specifically binds to the polypeptide of claim 1.

17. A purified agonist of the polypeptide of claim 1.

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of TRNSFS, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

20. A method for treating or preventing a disorder associated with increased expression or activity of TRNSFS, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

21. A polypeptide fragment of claim 1, wherein the fragment is an enzymatically active fragment.

```
1    MAEDSESAASQQSLELDDQDTCGIDGDNEEETEHA  1632930
1    MMEGNG----------NGHEHCS-DCENEEDNSYN  GI 2443814

36   KG--SPGGYLGAKKKKKKQKRKKEKPNSGGTKSDS  1632930
25   RGGLSPANDTGAKKKKKKQKKKKEK----GSETDS  GI 2443814

69   ASDSQEIKIQQPSKNPSVPMQKLQDIQRAMELLSA  1632930
56   AQD-------QPVKMNSLPAERIQEIQKAIELFSV  GI 2443814

104  CQGPARNIDEAAKHRYQFWDTQPVPKLDEVITSHG  1632930
84   GQGPAKTMEEASKRSYQFWDTQPVPKLGEVVNTHG  GI 2443814

139  AIEPDKVNVRQEPYSLPQGFMWDTLDLSDAEVLKE  1632930
119  PVEPDKDNIRQEPYTLPQGFTWDALDLGDRGVLKE  GI 2443814

174  LYTLLNENYVEDDDNMFRFDYSPEFLLWALRPPGW  1632930
154  LYTLLNENYVEDDDNMFRFDYSPEFLLWALRPPGW  GI 2443814

209  LLQWHCGVRVSSNKKLVGFISAIPANIRIYDSVKK  1632930
189  LPQWHCGVRVVSSRKLVGFISAIPANIHIYDTEKK  GI 2443814

244  MVEINFLCVHKKLRSKRVAPVLIREITRRVNLEGI  1632930
224  MVEINFLCVHKKLRSKRVAPVLIREITRRVHLEGI  GI 2443814
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FIGURE 1A

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279 FQAVYTAGVVLPKPIATCRYWHRSLNPRKLVEVKF 1632930
259 FQAVYTAGVVLPKPVGTCRYWHRSLNPRKLIEVKF GI 2443814

314 SHLSRNMTLQRTMKLYRLPDVTKTSGLRPMEPKDI 1632930
294 SHLSRNMTMQRTMKLYRLPETPKTAGLRPMETKDI GI 2443814

349 KSVRELINTYLKQFHLAPVMDEEEVAHWFLPREHI 1632930
329 PVVHQLLTRYLKQFHLTPVMSQEEVEHWFYPQENI GI 2443814

384 IDTFVVESPNGKLTDFLSFYTLPSTVMHHPAHKSL 1632930
364 IDTFVVENANGEVTDFLSFYTLPSTIMNHPTHKSL GI 2443814

419 KAAYSFYNIHTETPLLDLMSDALILAKSKGFDVFN 1632930
399 KAAYSFYNVHTQTPLLDLMSDALVLAKMKGFDVFN GI 2443814

454 ALDLMENKTFLEKLKFGIGDGNLQYYLYNWRCPGT 1632930
434 ALDLMENKTFLEKLKFGIGDGNLQYYLYNWKCPSM GI 2443814

489 DSEKVGLVLQ 1632930
469 GAEKVGLVLQ GI 2443814
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FIGURE 1B

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1    M - - - - - - - - K A L I L V G G Y G T  2682663
1    M - - - - - - - - K A L I L V G G F G T  g2642159
1    M V V S P L P S M K A L I L V G G Y G T  g2804432

13   R L R P L T L S T P K P L V D F C N K P  2682663
13   R L R P L T L S F P K P L V D F A N K P  g2642159
21   R L R P L T L T Q P K P L V E F A N K P  g2804432

33   I L L H Q V E A L A A A G V D H V I L A  2682663
33   M I L H Q I E A L K A V G V D E V V L A  g2642159
41   M M L H Q M E A L A E V G V D T V V L A  g2804432

53   V S Y M S Q V L E K E M K A Q E Q R L G  2682663
53   I N Y Q P E V M L N F L K D F E T K L E  g2642159
61   V S Y R A E Q L E Q E M T V H A D R L G  g2804432

73   I R I S M S H E E E P L G T A G P L A L  2682663
73   I K I T C S Q E T E P L G T A G P L A L  g2642159
81   V K L I F S L E E E P L G T A G P L A L  g2804432

93   A R - D L L S E T A D P F F V L N S D V  2682663
93   A R D K L L D G S G E P F F V L N S D V  g2642159
101  A R - K H L - E G D A P F F V L N S D V  g2804432
```

FIGURE 2A

```
112 I C D F P F Q A M V Q F H R H H G Q E G 2682663
113 I S E Y P L K E M L E F H K S H G G E A g2642159
119 I C D F P F K Q M V E F H K N H G K E G g2804432

132 S I L V T K V E E P S K Y G V V V C E A 2682663
133 S I M V T K V D E P S K Y G V V V M E E g2642159
139 T I A V T K V E E P S K Y G V V V F D Q g2804432

152 D T G R I H R F V E K P Q V F V S N K I 2682663
153 S T G R V E K F V E K P K L Y V G N K I g2642159
159 D K G K I D D F V E K P Q E Y V G N K I g2804432

172 N A G M Y I L S P A V L R R I Q L Q P T 2682663
173 N A G I Y L L N P S V L D K I E L R P T g2642159
179 N A G L Y I F S S K I L D R I P L K P T g2804432

192 S I E K E V F P I M A K E G Q L Y A M E 2682663
193 S I E K E T F P K I A A A Q G L Y A M V g2642159
199 S I E K E I F P E M A F S G N L Y A F V g2804432

212 L Q G F W M D I G Q P K D F L T G M C L 2682663
213 L P G F W M D I G Q P R D Y I T G L R L g2642159
219 L P G F W M D V G Q P K D F L K G M S L g2804432
```

FIGURE 2B

```
232 F L Q S L R Q K Q P E R L C S G P G I V 2682663
233 Y L D S L R K K S P A K L T S G P H I V g2642159
239 F L N H C H T T K S D K L E T G S N I H g2804432

252 - - - - - - G N V L V D P S A R I G Q N 2682663
253 - - - - - - G N V L V D E T A T I G E G g2642159
259 P T A T I R G N V M V D P S A T V G E N g2804432

266 C S I G P N V S L G P G V V V E D G V C 2682663
267 C L I G P D V A I G P G C I V E S G V R g2642159
279 C V I G P D V V I G P R V K I E G G V R g2804432

286 I R R C T V L R D A R I R S H S W L E S 2682663
287 L S R C T V M R G V R I K K H A C I S S g2642159
299 I L H S T I L S D S S I G N Y S W V S G g2804432

306 C I V G W R C R V G Q W V R M E N V T V 2682663
307 S I I G W H S T V G Q W A R I E N M T I g2642159
319 S I V G R K C H I G S W V R I E N I C V g2804432

326 L G E D V I V N D E L Y L N G A S V L P 2682663
327 L G E D V H V S D E I Y S N G G V V L P g2642159
339 I G D D V V V K D E L Y L N G A S V L P g2804432
```

FIGURE 2C

346	H	K	S	I	G	E	S	V	P	E	P	R	I	I	M	2682663
347	H	K	E	I	K	S	N	I	L	K	P	E	I	V	M	g2642159
359	H	K	S	I	A	V	N	V	P	S	K	D	I	I	M	g280443

FIGURE 2D

SEQUENCE LISTING

<110> INCYTE PHARMACEUTICALS, INC.
TANG, Y. Tom
CORLEY, Neil C.
GUEGLER, Karl J.
BAUGHN, Mariah R.
LAL, Preeti
YUE, Henry
HILLMAN, Jennifer L.
AZIMZAI, Yalda

<120> HUMAN TRANSFERASE PROTEINS

<130> PF-0592 PCT

<140> To Be Assigned
<141> Herewith

<150> 09/150,657; unassigned; 09/186,779; unassigned; 60/133,642
<151> 1998-09-10; 1998-09-10; 1998-11-04; 1998-11-04; 1999-05-11

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                 20                  25                  30
Glu Thr Glu His Ala Lys Gly Ser Pro Gly Gly Tyr Leu Gly Ala
                 35                  40                  45
Lys Lys Lys Lys Lys Lys Gln Lys Arg Lys Lys Glu Lys Pro Asn
                 50                  55                  60
Ser Gly Gly Thr Lys Ser Asp Ser Ala Ser Asp Ser Gln Glu Ile
                 65                  70                  75
Lys Ile Gln Gln Pro Ser Lys Asn Pro Ser Val Pro Met Gln Lys
                 80                  85                  90
Leu Gln Asp Ile Gln Arg Ala Met Glu Leu Leu Ser Ala Cys Gln
                 95                 100                 105
Gly Pro Ala Arg Asn Ile Asp Glu Ala Ala Lys His Arg Tyr Gln
                110                 115                 120
Phe Trp Asp Thr Gln Pro Val Pro Lys Leu Asp Glu Val Ile Thr
                125                 130                 135
Ser His Gly Ala Ile Glu Pro Asp Lys Val Asn Val Arg Gln Glu
                140                 145                 150
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Pro Tyr Ser Leu Pro Gln Gly Phe Met Trp Asp Thr Leu Asp Leu
                155                 160                 165
Ser Asp Ala Glu Val Leu Lys Glu Leu Tyr Thr Leu Leu Asn Glu
                170                 175                 180
Asn Tyr Val Glu Asp Asp Asp Asn Met Phe Arg Phe Asp Tyr Ser
                185                 190                 195
Pro Glu Phe Leu Leu Trp Ala Leu Arg Pro Pro Gly Trp Leu Leu
                200                 205                 210
Gln Trp His Cys Gly Val Arg Val Ser Ser Asn Lys Lys Leu Val
                215                 220                 225
Gly Phe Ile Ser Ala Ile Pro Ala Asn Ile Arg Ile Tyr Asp Ser
                230                 235                 240
Val Lys Lys Met Val Glu Ile Asn Phe Leu Cys Val His Lys Lys
                245                 250                 255
Leu Arg Ser Lys Arg Val Ala Pro Val Leu Ile Arg Glu Ile Thr
                260                 265                 270
Arg Arg Val Asn Leu Glu Gly Ile Phe Gln Ala Val Tyr Thr Ala
                275                 280                 285
Gly Val Val Leu Pro Lys Pro Ile Ala Thr Cys Arg Tyr Trp His
                290                 295                 300
Arg Ser Leu Asn Pro Arg Lys Leu Val Glu Val Lys Phe Ser His
                305                 310                 315
Leu Ser Arg Asn Met Thr Leu Gln Arg Thr Met Lys Leu Tyr Arg
                320                 325                 330
Leu Pro Asp Val Thr Lys Thr Ser Gly Leu Arg Pro Met Glu Pro
                335                 340                 345
Lys Asp Ile Lys Ser Val Arg Glu Leu Ile Asn Thr Tyr Leu Lys
                350                 355                 360
Gln Phe His Leu Ala Pro Val Met Asp Glu Glu Glu Val Ala His
                365                 370                 375
Trp Phe Leu Pro Arg Glu His Ile Ile Asp Thr Phe Val Val Glu
                380                 385                 390
Ser Pro Asn Gly Lys Leu Thr Asp Phe Leu Ser Phe Tyr Thr Leu
                395                 400                 405
Pro Ser Thr Val Met His His Pro Ala His Lys Ser Leu Lys Ala
                410                 415                 420
Ala Tyr Ser Phe Tyr Asn Ile His Thr Glu Thr Pro Leu Leu Asp
                425                 430                 435
Leu Met Ser Asp Ala Leu Ile Leu Ala Lys Ser Lys Gly Phe Asp
                440                 445                 450
Val Phe Asn Ala Leu Asp Leu Met Glu Asn Lys Thr Phe Leu Glu
                455                 460                 465
Lys Leu Lys Phe Gly Ile Gly Asp Gly Asn Leu Gln Tyr Tyr Leu
                470                 475                 480
Tyr Asn Trp Arg Cys Pro Gly Thr Asp Ser Glu Lys Val Gly Leu
                485                 490                 495
Val Leu Gln

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20 25 30
Lys Pro Ile Leu Leu His Gln Val Glu Ala Leu Ala Ala Ala Gly
35 40 45
Val Asp His Val Ile Leu Ala Val Ser Tyr Met Ser Gln Val Leu
50 55 60
Glu Lys Glu Met Lys Ala Gln Glu Gln Arg Leu Gly Ile Arg Ile
65 70 75
Ser Met Ser His Glu Glu Glu Pro Leu Gly Thr Ala Gly Pro Leu
80 85 90
Ala Leu Ala Arg Asp Leu Leu Ser Glu Thr Ala Asp Pro Phe Phe
95 100 105
Val Leu Asn Ser Asp Val Ile Cys Asp Phe Pro Phe Gln Ala Met
110 115 120
Val Gln Phe His Arg His His Gly Gln Glu Gly Ser Ile Leu Val
125 130 135
Thr Lys Val Glu Glu Pro Ser Lys Tyr Gly Val Val Val Cys Glu
140 145 150
Ala Asp Thr Gly Arg Ile His Arg Phe Val Glu Lys Pro Gln Val
155 160 165
Phe Val Ser Asn Lys Ile Asn Ala Gly Met Tyr Ile Leu Ser Pro
170 175 180
Ala Val Leu Arg Arg Ile Gln Leu Gln Pro Thr Ser Ile Glu Lys
185 190 195
Glu Val Phe Pro Ile Met Ala Lys Glu Gly Gln Leu Tyr Ala Met
200 205 210
Glu Leu Gln Gly Phe Trp Met Asp Ile Gly Gln Pro Lys Asp Phe
215 220 225
Leu Thr Gly Met Cys Leu Phe Leu Gln Ser Leu Arg Gln Lys Gln
230 235 240
Pro Glu Arg Leu Cys Ser Gly Pro Gly Ile Val Gly Asn Val Leu
245 250 255
Val Asp Pro Ser Ala Arg Ile Gly Gln Asn Cys Ser Ile Gly Pro
260 265 270
Asn Val Ser Leu Gly Pro Gly Val Val Val Glu Asp Gly Val Cys
275 280 285
Ile Arg Arg Cys Thr Val Leu Arg Asp Ala Arg Ile Arg Ser His
290 295 300
Ser Trp Leu Glu Ser Cys Ile Val Gly Trp Arg Cys Arg Val Gly
305 310 315
Gln Trp Val Arg Met Glu Asn Val Thr Val Leu Gly Glu Asp Val
320 325 330

Ile Val Asn Asp Glu Leu Tyr Leu Asn Gly Ala Ser Val Leu Pro
335 340 345
His Lys Ser Ile Gly Glu Ser Val Pro Glu Pro Arg Ile Ile Met
350 355 360

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35 40 45
Lys Asp Tyr Glu Ala Cys Lys Ala Val Ile Lys Glu Gln Leu Gln
50 55 60
Glu Thr Gln Gly Leu Cys Glu Tyr Ala Ile Tyr Val Gln Ala Leu
65 70 75
Ile Phe Arg Leu Glu Gly Asn Ile Gln Glu Ser Leu Glu Leu Phe
80 85 90
Gln Thr Cys Ala Val Leu Ser Pro Gln Ser Ala Asp Asn Leu Lys
95 100 105
Gln Val Ala Arg Ser Leu Phe Leu Leu Gly Lys His Lys Ala Ala
110 115 120
Ile Glu Val Tyr Asn Glu Ala Ala Lys Leu Asn Gln Lys Asp Trp
125 130 135
Glu Ile Ser His Asn Leu Gly Val Cys Tyr Ile Tyr Leu Lys Gln
140 145 150
Phe Asn Lys Ala Gln Asp Gln Leu His Asn Ala Leu Asn Leu Asn
155 160 165
Arg His Asp Leu Thr Tyr Ile Met Leu Gly Lys Ile His Leu Leu
170 175 180
Glu Gly Asp Leu Asp Lys Ala Ile Glu Val Tyr Lys Lys Ala Val
185 190 195
Glu Phe Ser Pro Glu Asn Thr Glu Leu Leu Thr Thr Leu Gly Leu
200 205 210
Leu Tyr Leu Gln Leu Gly Ile Tyr Gln Lys Ala Phe Glu His Leu
215 220 225
Gly Asn Ala Leu Thr Tyr Asp Pro Thr Asn Tyr Lys Ala Ile Leu
230 235 240
Ala Ala Gly Ser Met Met Gln Thr His Gly Asp Phe Asp Val Ala
245 250 255
Leu Thr Lys Tyr Arg Val Val Ala Cys Ala Val Pro Glu Ser Pro
260 265 270
Pro Leu Trp Asn Asn Ile Gly Met Cys Phe Phe Gly Lys Lys Lys
275 280 285
Tyr Val Ala Ala Ile Ser Cys Leu Lys Arg Ala Asn Tyr Leu Ala
290 295 300
Pro Phe Asp Trp Lys Ile Leu Tyr Asn Leu Gly Leu Val His Leu
305 310 315
Thr Met Gln Gln Tyr Ala Ser Ala Phe His Phe Leu Ser Ala Ala
320 325 330
Ile Asn Phe Gln Pro Lys Met Gly Glu Leu Tyr Met Leu Leu Ala
335 340 345
Val Ala Leu Thr Asn Leu Glu Asp Thr Glu Asn Ala Lys Arg Ala
350 355 360
Tyr Ala Glu Ala Val His Leu Asp Lys Cys Asn Pro Leu Val Asn
365 370 375
Leu Asn Tyr Ala Val Leu Leu Tyr Asn Gln Gly Glu Lys Lys Asn
380 385 390

Ala Leu Ala Gln Tyr Gln Glu Met Glu Lys Lys Val Ser Leu Leu
395 400 405
Lys Asp Asn Ser Ser Leu Glu Phe Asp Ser Glu Met Val Glu Met
410 415 420
Ala Gln Lys Leu Gly Ala Ala Leu Gln Val Gly Glu Ala Leu Val
425 430 435
Trp Thr Lys Pro Val Lys Asp Pro Lys Ser Lys His Gln Thr Thr
440 445 450
Ser Thr Ser Lys Pro Ala Ser Phe Gln Gln Pro Leu Gly Ser Asn
455 460 465
Gln Ala Leu Gly Gln Ala Met Ser Ser Ala Ala Ala Tyr Arg Thr
470 475 480
Leu Pro Ser Gly Ala Gly Gly Thr Ser Gln Phe Thr Lys Pro Pro
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Tyr Pro Gln His Tyr Tyr Gly Asp Leu Glu Tyr Val Leu Ile Pro
35 40 45
His Gly Ile Ile Val Asp Arg Ile Glu Arg Leu Ala Lys Asp Ile
50 55 60
Met Lys Asp Ile Gly Tyr Ser Asp Ile Met Val Leu Cys Val Leu
65 70 75
Lys Gly Gly Tyr Lys Phe Cys Ala Asp Leu Val Glu His Leu Lys
80 85 90
Asn Ile Ser Arg Asn Ser Asp Arg Phe Val Ser Met Lys Val Asp
95 100 105
Phe Ile Arg Leu Lys Ser Tyr Arg Asn Asp Gln Ser Met Gly Glu
110 115 120
Met Gln Ile Ile Gly Gly Gly Asp Leu Ser Thr Leu Ala Gly Lys
125 130 135
Asn Val Leu Ile Val Glu Asp Val Val Gly Thr Gly Arg Thr Met
140 145 150
Lys Ala Leu Leu Ser Asn Ile Glu Lys Tyr Arg Pro Asn Met Ile
155 160 165
Lys Val Ala Ser Leu Leu Val Lys Arg Thr Ser Arg Ser Asp Gly
170 175 180
Phe Arg Pro Asp Tyr Ala Gly Phe Glu Ile Pro Asn Leu Phe Val
185 190 195
Val Gly Tyr Ala Leu Asp Tyr Asn Glu Tyr Phe Arg Asp Leu Asn

200 205 210
His Ile Cys Val Ile Asn Glu His Gly Lys Glu Lys Tyr Arg Val
215 220 225

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Gly Glu Thr Val Lys Ala Gly Asp Arg Asp Pro Leu Gly Asn Asp
20 25 30
Cys Pro Glu Gln Asp Arg Leu Pro Gln Arg Ser Trp Arg Gln Lys
35 40 45
Cys Ala Ser Tyr Val Leu Ala Leu Arg Pro Trp Ser Phe Ser Ala
50 55 60
Ser Leu Thr Pro Val Ala Leu Gly Ser Ala Leu Ala Tyr Arg Ser
65 70 75
His Gly Val Leu Asp Pro Arg Leu Leu Val Gly Cys Ala Val Ala
80 85 90
Val Leu Ala Val His Gly Ala Gly Asn Leu Val Asn Thr Tyr Tyr
95 100 105
Asp Phe Ser Lys Gly Ile Asp His Lys Lys Ser Asp Asp Arg Thr
110 115 120
Leu Val Asp Arg Ile Leu Glu Pro Gln Asp Val Val Arg Phe Gly
125 130 135
Val Phe Leu Tyr Thr Leu Gly Cys Val Cys Ala Ala Cys Leu Tyr
140 145 150
Tyr Leu Ser Pro Leu Lys Leu Glu His Leu Ala Leu Ile Tyr Phe
155 160 165
Gly Gly Leu Ser Gly Ser Phe Leu Tyr Thr Gly Gly Ile Gly Phe
170 175 180
Lys Tyr Val Ala Leu Gly Asp Leu Ile Ile Leu Ile Thr Phe Gly
185 190 195
Pro Leu Ala Val Met Phe Ala Tyr Ala Ile Gln Val Gly Ser Leu
200 205 210
Ala Ile Phe Pro Leu Val Tyr Ala Ile Pro Leu Ala Leu Ser Thr
215 220 225
Glu Ala Ile Leu His Ser Asn Asn Thr Arg Asp Met Glu Ser Asp
230 235 240
Arg Glu Ala Gly Ile Val Thr Leu Ala Ile Leu Ile Gly Pro Thr
245 250 255
Phe Ser Tyr Ile Leu Tyr Asn Thr Leu Leu Phe Leu Pro Tyr Leu
260 265 270
Val Phe Ser Ile Leu Ala Thr His Cys Thr Ile Ser Leu Ala Leu
275 280 285
Pro Leu Leu Thr Ile Pro Met Ala Phe Ser Leu Glu Arg Gln Phe
290 295 300
Arg Ser Gln Ala Phe Asn Lys Leu Pro Gln Arg Thr Ala Lys Leu
305 310 315

Asn Leu Leu Leu Gly Leu Phe Tyr Val Phe Gly Ile Ile Leu Ala
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Pro Ala Gly Ser Leu Pro Lys Ile
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20 25 30
Gly Gln Val Val Gly Thr Arg Gly Gly Phe Arg Gly Cys Thr Val
35 40 45
Trp Leu Thr Gly Leu Ser Gly Ala Gly Lys Thr Thr Ile Ser Phe
50 55 60
Ala Leu Glu Glu Tyr Leu Val Ser His Ala Ile Pro Cys Tyr Ser
65 70 75
Leu Asp Gly Asp Asn Val Arg His Gly Leu Asn Arg Asn Leu Gly
80 85 90
Ser Ser Pro Gly Asp Arg Glu Glu Asn Ile Arg Arg Ile Ala Glu
95 100 105
Val Ala Lys Leu Phe Ala Asp Ala Gly Leu Val Cys Ile Thr Ser
110 115 120
Phe Ile Ser Pro Phe Ala Lys Asp Arg Glu Asn Ala Arg Lys Ile
125 130 135
His Glu Ser Ala Gly Leu Pro Phe Phe Glu Ile Phe Val Asp Ala
140 145 150
Pro Leu Asn Ile Cys Glu Ser Arg Asp Val Lys Gly Leu Tyr Lys
155 160 165
Arg Ala Arg Ala Gly Glu Ile Lys Gly Phe Thr Gly Ile Asp Ser
170 175 180
Asp Tyr Glu Lys Pro Glu Thr Pro Glu Arg Val Leu Lys Thr Asn
185 190 195
Leu Ser Thr Val Ser Asp Cys Val His Gln Val Val Glu Leu Leu
200 205 210
Gln Glu Gln Asn Ile Val Pro Tyr Thr Ile Ile Lys Asp Ile His
215 220 225
Glu Leu Phe Val Pro Glu Asn Lys Leu Asp His Val Arg Ala Glu
230 235 240
Ala Glu Thr Leu Pro Ser Leu Ser Ile Thr Lys Leu Asp Leu Gln
245 250 255
Trp Val Gln Val Leu Ser Glu Gly Trp Ala Thr Pro Leu Lys Gly
260 265 270
Phe Met Arg Glu Lys Glu Tyr Leu Gln Val Met His Phe Asp Thr
275 280 285
Leu Leu Asp Gly Met Ala Leu Pro Asp Gly Val Ile Asn Met Ser
290 295 300
Ile Pro Ile Val Leu Pro Val Ser Ala Glu Asp Lys Thr Arg Leu

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                    305                 310                 315
Glu Gly Cys Ser Lys Phe Val Leu Ala His Gly Gly Arg Arg Val
                    320                 325                 330
Ala Ile Leu Arg Asp Ala Glu Phe Tyr Glu His Arg Lys Glu Glu
                    335                 340                 345
Arg Cys Ser Arg Val Trp Gly Thr Thr Cys Thr Lys His Pro His
                    350                 355                 360
Ile Lys Met Val Met Glu Ser Gly Asp Trp Leu Val Gly Gly Asp
                    365                 370                 375
Leu Gln Val Leu Glu Lys Ile Arg Trp Asn Asp Gly Leu Asp Gln
                    380                 385                 390
Tyr Arg Leu Thr Pro Leu Glu Leu Lys Gln Lys Cys Lys Glu Met
                    395                 400                 405
Asn Ala Asp Ala Val Phe Ala Phe Gln Leu Arg Asn Pro Val His
                    410                 415                 420
Asn Gly His Ala Leu Leu Met Gln Asp Thr Arg Arg Arg Leu Leu
                    425                 430                 435
Glu Arg Gly Tyr Lys His Pro Val Leu Leu Leu His Pro Leu Gly
                    440                 445                 450
Gly Trp Thr Lys Asp Asp Asp Val Pro Leu Asp Trp Arg Met Lys
                    455                 460                 465
Gln His Ala Ala Val Leu Glu Glu Gly Val Leu Asp Pro Lys Ser
                    470                 475                 480
Thr Ile Val Ala Ile Phe Pro Ser Pro Met Leu Tyr Ala Gly Pro
                    485                 490                 495
Thr Glu Val Gln Trp His Cys Arg Ser Arg Met Ile Ala Gly Ala
                    500                 505                 510
Asn Phe Tyr Ile Val Gly Arg Asp Pro Ala Gly Met Pro His Pro
                    515                 520                 525
Glu Thr Lys Lys Asp Leu Tyr Glu Pro Thr His Gly Gly Lys Val
                    530                 535                 540
Leu Ser Met Ala Pro Gly Leu Thr Ser Val Glu Ile Ile Pro Phe
                    545                 550                 555
Arg Val Ala Ala Tyr Asn Lys Ala Lys Lys Ala Met Asp Phe Tyr
                    560                 565                 570

Asp Pro Ala Arg His Asn Glu Phe Asp Phe Ile Ser Gly Thr Arg
                    575                 580                 585
Met Arg Lys Leu Ala Arg Glu Gly Glu Asn Pro Pro Asp Gly Phe
                    590                 595                 600
Met Ala Pro Lys Ala Trp Lys Val Leu Thr Asp Tyr Tyr Arg Ser
                    605                 610                 615
Leu Glu Lys Asn


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                20                  25                  30
Cys Arg Gly Lys Met Glu Glu Ile Ala Asn Phe Pro Val Arg Pro
                35                  40                  45
Ser Asp Val Trp Ile Val Thr Tyr Pro Lys Ser Gly Thr Ser Leu
                50                  55                  60
Leu Gln Glu Val Val Tyr Leu Val Ser Gln Gly Ala Asp Pro Asp
                65                  70                  75
Glu Ile Gly Leu Met Asn Ile Asp Glu Gln Leu Pro Val Leu Glu
                80                  85                  90
Tyr Pro Gln Pro Gly Leu Asp Ile Ile Lys Glu Leu Thr Ser Pro
                95                  100                 105
Arg Leu Ile Lys Ser His Leu Pro Tyr Arg Phe Leu Pro Ser Asp
                110                 115                 120
Leu His Asn Gly Asp Ser Lys Val Ile Tyr Met Ala Arg Asn Pro
                125                 130                 135
Lys Asp Leu Val Val Ser Tyr Tyr Gln Phe His Arg Ser Leu Arg
                140                 145                 150
Thr Met Ser Tyr Arg Gly Thr Phe Gln Glu Phe Cys Arg Arg Phe
                155                 160                 165
Met Asn Asp Lys Leu Gly Tyr Gly Ser Trp Phe Glu His Val Gln
                170                 175                 180
Glu Phe Trp Glu His Arg Met Asp Ser Asn Val Leu Phe Leu Lys
                185                 190                 195
Tyr Glu Asp Met His Arg Asp Leu Val Thr Met Val Glu Gln Leu
                200                 205                 210
Ala Arg Phe Leu Gly Val Ser Cys Asp Lys Ala Gln Leu Glu Ala
                215                 220                 225
Leu Thr Glu His Cys His Gln Leu Val Asp Gln Cys Cys Asn Ala
                230                 235                 240
Glu Ala Leu Pro Val Gly Arg Gly Arg Val Gly Leu Trp Lys Asp
                245                 250                 255


Ile Phe Thr Val Ser Met Asn Glu Lys Phe Asp Leu Val Tyr Lys
                260                 265                 270
Gln Lys Met Gly Lys Cys Asp Leu Thr Phe Asp Phe Tyr Leu
                275                 280
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                20                  25                  30
Asn Pro Leu Tyr Trp Asn Val Val Ala Arg Trp Glu His Lys Thr
                35                  40                  45
Arg Lys Leu Ser Arg Ala Phe Gly Ser Pro Tyr Leu Ala Cys Tyr
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                50                  55                  60
Ser Leu Ser Val Thr Ile Leu Leu Leu Asn Phe Leu Arg Ser His
                65                  70                  75
Cys Phe Thr Gln Ala Met Leu Ser Gln Pro Arg Met Glu Ser Leu
                80                  85                  90
Asp Thr Pro Ala Ala Tyr Ser Leu Gly Leu Ala Leu Leu Gly Leu
                95                  100                 105
Gly Val Val Leu Val Leu Ser Ser Phe Phe Ala Leu Gly Phe Ala
                110                 115                 120
Gly Thr Phe Leu Gly Asp Tyr Phe Gly Ile Leu Lys Glu Ala Arg
                125                 130                 135
Val Thr Val Phe Pro Phe Asn Ile Leu Asp Asn Pro Met Tyr Trp
                140                 145                 150
Gly Ser Thr Ala Asn Tyr Leu Gly Trp Ala Ile Met His Ala Ser
                155                 160                 165
Pro Thr Gly Leu Leu Leu Thr Val Leu Val Ala Leu Thr Tyr Ile
                170                 175                 180
Val Ala Leu Leu Tyr Glu Glu Pro Phe Thr Ala Glu Ile Tyr Arg
                185                 190                 195
Gln Lys Ala Ser Gly Ser His Lys Arg Ser
                200                 205


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                20                  25                  30
Ala Ala His Phe Tyr Leu His Thr Ser Phe Ser Arg Pro His Thr
                35                  40                  45
Gly Pro Pro Leu Pro Thr Pro Gly Pro Asp Arg Asp Arg Glu Leu
                50                  55                  60
Thr Ala Asp Ser Asp Val Asp Glu Phe Leu Asp Lys Phe Leu Ser
                65                  70                  75
Ala Gly Val Lys Gln Ser Asp Leu Pro Arg Lys Glu Thr Glu Gln
                80                  85                  90
Pro Pro Ala Pro Gly Ser Met Glu Glu Ser Val Arg Gly Tyr Asp
                95                  100                 105
Trp Ser Pro Arg Asp Ala Arg Arg Ser Pro Asp Gln Gly Arg Gln
                110                 115                 120
Gln Ala Glu Arg Arg Ser Val Leu Arg Gly Phe Cys Ala Asn Ser
                125                 130                 135
Ser Leu Ala Phe Pro Thr Lys Glu Arg Ala Phe Asp Asp Ile Pro
                140                 145                 150
Asn Ser Glu Leu Ser His Leu Ile Val Asp Asp Arg His Gly Ala
                155                 160                 165
Ile Tyr Cys Tyr Val Pro Lys Val Ala Cys Thr Asn Trp Lys Arg
                170                 175                 180
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Val Met Ile Val Leu Ser Gly Ser Leu Leu His Arg Gly Ala Pro
185 190 195
Tyr Arg Asp Pro Leu Arg Ile Pro Arg Glu His Val His Asn Ala
200 205 210
Ser Ala His Leu Thr Phe Asn Lys Phe Trp Arg Arg Tyr Gly Lys
215 220 225
Leu Ser Arg His Leu Met Lys Val Lys Leu Lys Lys Tyr Thr Lys
230 235 240
Phe Leu Phe Val Arg Asp Pro Phe Val Arg Leu Ile Ser Ala Phe
245 250 255
Arg Ser Lys Phe Glu Leu Glu Asn Glu Glu Phe Tyr Arg Lys Phe
260 265 270
Ala Val Pro Met Leu Arg Leu Tyr Ala Asn His Thr Ser Leu Pro
275 280 285
Ala Ser Ala Arg Glu Ala Phe Arg Ala Gly Leu Lys Val Ser Phe
290 295 300
Ala Asn Phe Ile Gln Tyr Leu Leu Asp Pro His Thr Glu Lys Leu
305 310 315
Ala Pro Phe Asn Glu His Trp Arg Gln Val Tyr Arg Leu Cys His
320 325 330
Pro Cys Gln Ile Asp Tyr Asp Phe Val Gly Lys Leu Glu Thr Leu
335 340 345
Asp Glu Asp Ala Ala Gln Leu Leu Gln Leu Leu Gln Val Asp Arg
350 355 360
Gln Leu Arg Phe Pro Pro Ser Tyr Arg Asn Arg Thr Ala Ser Ser
365 370 375
Trp Glu Glu Asp Trp Phe Ala Lys Ile Pro Leu Ala Trp Arg Gln
380 385 390

Gln Leu Tyr Lys Leu Tyr Glu Ala Asp Phe Val Leu Phe Gly Tyr
395 400 405
Pro Lys Pro Glu Asn Leu Leu Arg Asp
410

<210> 10
<211> 660
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2153162CD1

<400> 10
Met Asp Asp Trp Lys Pro Ser Pro Leu Ile Lys Pro Phe Gly Ala
1 5 10 15
Arg Lys Lys Arg Ser Trp Tyr Leu Thr Trp Lys Tyr Lys Leu Thr
20 25 30
Asn Gln Arg Ala Leu Arg Arg Phe Cys Gln Thr Gly Ala Val Leu
35 40 45
Phe Leu Leu Val Thr Val Ile Val Asn Ile Lys Leu Ile Leu Asp
50 55 60
Thr Arg Arg Ala Ile Ser Glu Ala Asn Glu Asp Pro Glu Pro Glu
65 70 75
Gln Asp Tyr Asp Glu Ala Leu Gly Arg Leu Glu Pro Pro Arg Arg

```
                    80                  85                  90
Arg Gly Ser Gly Pro Arg Arg Val Leu Asp Val Glu Val Tyr Ser
                    95                 100                 105
Ser Arg Ser Lys Val Tyr Val Ala Val Asp Gly Thr Thr Val Leu
                   110                 115                 120
Glu Asp Glu Ala Arg Glu Gln Gly Arg Gly Ile His Val Ile Val
                   125                 130                 135
Leu Asn Gln Ala Thr Gly His Val Met Ala Lys Arg Val Phe Asp
                   140                 145                 150
Thr Tyr Ser Pro His Glu Asp Glu Ala Met Val Leu Phe Leu Asn
                   155                 160                 165
Met Val Ala Pro Gly Arg Val Leu Ile Cys Thr Val Lys Asp Glu
                   170                 175                 180
Gly Ser Phe His Leu Lys Asp Thr Ala Lys Ala Leu Leu Arg Ser
                   185                 190                 195
Leu Gly Ser Gln Ala Gly Pro Ala Leu Gly Trp Arg Asp Thr Trp
                   200                 205                 210
Ala Phe Val Gly Arg Lys Gly Gly Pro Val Phe Gly Glu Lys His
                   215                 220                 225
Ser Lys Ser Pro Ala Leu Ser Ser Trp Gly Asp Pro Val Leu Leu
                   230                 235                 240
Lys Thr Asp Val Pro Leu Ser Ser Ala Glu Glu Ala Glu Cys His
                   245                 250                 255
Trp Ala Asp Thr Glu Leu Asn Arg Arg Arg Arg Arg Phe Cys Ser
                   260                 265                 270
Lys Val Glu Gly Tyr Gly Ser Val Cys Ser Cys Lys Asp Pro Thr
                   275                 280                 285

Pro Ile Glu Phe Ser Pro Asp Pro Leu Pro Asp Asn Lys Val Leu
                   290                 295                 300
Asn Val Pro Val Ala Val Ile Ala Gly Asn Arg Pro Asn Tyr Leu
                   305                 310                 315
Tyr Arg Met Leu Arg Ser Leu Leu Ser Ala Gln Gly Val Ser Pro
                   320                 325                 330
Gln Met Ile Thr Val Phe Ile Asp Gly Tyr Tyr Glu Glu Pro Met
                   335                 340                 345
Asp Val Val Ala Leu Phe Gly Leu Arg Gly Ile Gln His Thr Pro
                   350                 355                 360
Ile Ser Ile Lys Asn Ala Arg Val Ser Gln His Tyr Lys Ala Ser
                   365                 370                 375
Leu Thr Ala Thr Phe Asn Leu Phe Pro Glu Ala Lys Phe Ala Val
                   380                 385                 390
Val Leu Glu Glu Asp Leu Asp Ile Ala Val Asp Phe Phe Ser Phe
                   395                 400                 405
Leu Ser Gln Ser Ile His Leu Leu Glu Glu Asp Asp Ser Leu Tyr
                   410                 415                 420
Cys Ile Ser Ala Trp Asn Asp Gln Gly Tyr Glu His Thr Ala Glu
                   425                 430                 435
Asp Pro Ala Leu Leu Tyr Arg Val Glu Thr Met Pro Gly Leu Gly
                   440                 445                 450
Trp Val Leu Arg Arg Ser Leu Tyr Lys Glu Glu Leu Glu Pro Lys
                   455                 460                 465
Trp Pro Thr Pro Glu Lys Leu Trp Asp Trp Asp Met Trp Met Arg
                   470                 475                 480
Met Pro Glu Gln Arg Arg Gly Arg Glu Cys Ile Ile Pro Asp Val
                   485                 490                 495
Ser Arg Ser Tyr His Phe Gly Ile Val Gly Leu Asn Met Asn Gly
```

```
                500                     505                     510
Tyr Phe His Glu Ala Tyr Phe Lys Lys His Lys Phe Asn Thr Val
                515                     520                     525
Pro Gly Val Gln Leu Arg Asn Val Asp Ser Leu Lys Lys Glu Ala
                530                     535                     540
Tyr Glu Val Glu Val His Arg Leu Leu Ser Glu Ala Glu Val Leu
                545                     550                     555
Asp His Ser Lys Asn Pro Cys Glu Asp Ser Phe Leu Pro Asp Thr
                560                     565                     570
Glu Gly His Thr Tyr Val Ala Phe Ile Arg Met Glu Lys Asp Asp
                575                     580                     585
Asp Phe Thr Thr Trp Thr Gln Leu Ala Lys Cys Leu His Ile Trp
                590                     595                     600
Asp Leu Asp Val Arg Gly Asn His Arg Gly Leu Trp Arg Leu Phe
                605                     610                     615
Arg Lys Lys Asn His Phe Leu Val Val Gly Val Pro Ala Ser Pro
                620                     625                     630
Tyr Ser Val Lys Lys Pro Pro Ser Val Thr Pro Ile Phe Leu Glu
                635                     640                     645
Pro Pro Pro Lys Glu Glu Gly Ala Pro Gly Ala Pro Glu Gln Thr
                650                     655                     660


<210> 11
<211> 386
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2617407CD1

<400> 11
Met Leu Leu Pro Lys Lys Met Lys Leu Leu Leu Phe Leu Val Ser
 1               5                      10                      15
Gln Met Ala Ile Leu Ala Leu Phe Phe His Met Tyr Ser His Asn
                20                      25                      30
Ile Ser Ser Leu Ser Met Lys Ala Gln Pro Glu Arg Met His Val
                35                      40                      45
Leu Val Leu Ser Ser Trp Arg Ser Gly Ser Ser Phe Val Gly Gln
                50                      55                      60
Leu Phe Gly Gln His Pro Asp Val Phe Tyr Leu Met Glu Pro Ala
                65                      70                      75
Trp His Val Trp Met Thr Phe Lys Gln Ser Thr Ala Trp Met Leu
                80                      85                      90
His Met Ala Val Arg Asp Leu Ile Arg Ala Val Phe Leu Cys Asp
                95                      100                     105
Met Ser Val Phe Asp Ala Tyr Met Glu Pro Gly Pro Arg Arg Gln
                110                     115                     120
Ser Ser Leu Phe Gln Trp Glu Asn Ser Arg Ala Leu Cys Ser Ala
                125                     130                     135
Pro Ala Cys Asp Ile Ile Pro Gln Asp Glu Ser Ser Pro Gly Leu
                140                     145                     150
Thr Ala Gly Ser Cys Ala Val Asn Ser Pro Leu Lys Leu Leu Glu
                155                     160                     165
Lys Ala Cys Arg Ser Tyr Ser His Val Val Leu Lys Glu Val Arg
                170                     175                     180
```

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Phe Phe Asn Leu Gln Ser Leu Tyr Pro Leu Leu Lys Asp Pro Ser
                185                 190                 195
Leu Asn Leu His Ile Val His Leu Val Arg Asp Pro Arg Ala Val
                200                 205                 210
Phe Arg Ser Arg Glu Arg Thr Lys Gly Asp Leu Met Ile Asp Ser
                215                 220                 225
Arg Ile Val Met Gly Gln His Glu Gln Lys Leu Lys Lys Glu Asp
                230                 235                 240
Gln Pro Tyr Tyr Val Met Gln Val Ile Cys Gln Ser Gln Leu Glu
                245                 250                 255
Ile Tyr Lys Thr Ile Gln Ser Leu Pro Lys Ala Leu Gln Glu Arg
                260                 265                 270
Tyr Leu Leu Val Arg Tyr Glu Asp Leu Ala Arg Ala Pro Val Ala
                275                 280                 285
Gln Thr Ser Arg Met Tyr Glu Phe Val Gly Leu Glu Phe Leu Pro
                290                 295                 300
His Leu Gln Thr Trp Val His Asn Ile Thr Arg Gly Lys Gly Met
                305                 310                 315
Gly Asp His Ala Phe His Thr Asn Ala Arg Asp Ala Leu Asn Val
                320                 325                 330
Ser Gln Ala Trp Arg Trp Ser Leu Pro Tyr Glu Lys Val Ser Arg
                335                 340                 345
Leu Gln Lys Ala Cys Gly Asp Ala Met Asn Leu Leu Gly Tyr Arg
                350                 355                 360
His Val Arg Ser Glu Gln Glu Gln Arg Asn Leu Leu Leu Asp Leu
                365                 370                 375
Leu Ser Thr Trp Thr Val Pro Glu Gln Ile His
                380                 385


<210> 12
<211> 803
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2963717CD1

<400> 12
Met Ala Glu Ala His Gln Ala Val Gly Phe Arg Pro Ser Leu Thr
  1               5                  10                  15
Ser Asp Gly Ala Glu Val Glu Leu Ser Ala Pro Val Leu Gln Glu
                 20                  25                  30
Ile Tyr Leu Ser Gly Leu Arg Ser Trp Lys Arg His Leu Ser Arg
                 35                  40                  45
Phe Trp Asn Asp Phe Leu Thr Gly Val Phe Pro Ala Ser Pro Leu
                 50                  55                  60
Ser Trp Leu Phe Leu Phe Ser Ala Ile Gln Leu Ala Trp Phe Leu
                 65                  70                  75
Gln Leu Asp Pro Ser Leu Gly Leu Met Glu Lys Ile Lys Glu Leu
                 80                  85                  90
Leu Pro Asp Trp Gly Gly Gln His His Gly Leu Arg Gly Val Leu
                 95                 100                 105
Ala Ala Ala Leu Phe Ala Ser Cys Leu Trp Gly Ala Leu Ile Phe
                110                 115                 120
Thr Leu His Val Ala Leu Arg Leu Leu Leu Ser Tyr His Gly Trp
```

125 130 135
Leu Leu Glu Pro His Gly Ala Met Ser Ser Pro Thr Lys Thr Trp
140 145 150
Leu Ala Leu Val Arg Ile Phe Ser Gly Arg His Pro Met Leu Phe
155 160 165
Ser Tyr Gln Arg Ser Leu Pro Arg Gln Pro Val Pro Ser Val Gln
170 175 180
Asp Thr Val Arg Lys Tyr Leu Glu Ser Val Arg Pro Ile Leu Ser
185 190 195
Asp Glu Asp Phe Asp Trp Thr Ala Val Leu Ala Gln Glu Phe Leu
200 205 210
Arg Leu Gln Ala Ser Leu Leu Gln Trp Tyr Leu Arg Leu Lys Ser
215 220 225
Trp Trp Ala Ser Asn Tyr Val Ser Asp Trp Trp Glu Glu Phe Val
230 235 240
Tyr Leu Arg Ser Arg Asn Pro Leu Met Val Asn Ser Asn Tyr Tyr
245 250 255
Met Met Asp Phe Leu Tyr Val Thr Pro Thr Pro Leu Gln Ala Ala
260 265 270
Arg Ala Gly Asn Ala Val His Ala Leu Leu Leu Tyr Arg His Arg
275 280 285

Leu Asn Arg Gln Glu Ile Pro Pro Thr Leu Leu Met Gly Met Arg
290 295 300
Pro Leu Cys Ser Ala Gln Tyr Glu Lys Ile Phe Asn Thr Thr Arg
305 310 315
Ile Pro Gly Val Gln Lys Asp Tyr Ile Arg His Leu His Asp Ser
320 325 330
Gln His Val Ala Val Phe His Arg Gly Arg Phe Phe Arg Met Gly
335 340 345
Thr His Ser Arg Asn Ser Leu Leu Ser Pro Arg Ala Leu Glu Gln
350 355 360
Gln Phe Gln Arg Ile Leu Asp Asp Pro Ser Pro Ala Cys Pro His
365 370 375
Glu Glu His Leu Ala Ala Leu Thr Ala Ala Pro Arg Gly Thr Trp
380 385 390
Ala Gln Val Arg Thr Ser Leu Lys Thr Gln Ala Ala Glu Ala Leu
395 400 405
Glu Ala Val Glu Gly Ala Ala Phe Phe Val Ser Leu Asp Ala Glu
410 415 420
Pro Ala Gly Leu Thr Arg Glu Asp Pro Ala Ala Ser Leu Asp Ala
425 430 435
Tyr Ala His Ala Leu Leu Ala Gly Arg Gly His Asp Arg Trp Phe
440 445 450
Asp Lys Ser Phe Thr Leu Ile Val Phe Ser Asn Gly Lys Leu Gly
455 460 465
Leu Ser Val Glu His Ser Trp Ala Asp Cys Pro Ile Ser Gly His
470 475 480
Met Trp Glu Phe Thr Leu Ala Thr Glu Cys Phe Gln Leu Gly Tyr
485 490 495
Ser Thr Asp Gly His Cys Lys Gly His Pro Asp Pro Thr Leu Pro
500 505 510
Gln Pro Gln Arg Leu Gln Trp Asp Leu Pro Asp Gln Ile His Ser
515 520 525
Ser Ile Ser Leu Ala Leu Arg Gly Ala Lys Ile Leu Ser Glu Asn
530 535 540
Val Asp Cys His Val Val Pro Phe Ser Leu Phe Gly Lys Ser Phe

545 550 555
Ile Arg Arg Cys His Leu Ser Ser Asp Ser Phe Ile Gln Ile Ala
560 565 570
Leu Gln Leu Ala His Phe Arg Asp Arg Gly Gln Phe Cys Leu Thr
575 580 585
Tyr Glu Ser Ala Met Thr Arg Leu Phe Leu Glu Gly Arg Thr Glu
590 595 600
Thr Val Arg Ser Cys Thr Arg Glu Ala Cys Asn Phe Val Arg Ala
605 610 615
Met Glu Asp Lys Glu Lys Thr Asp Pro Gln Cys Leu Ala Leu Phe
620 625 630
Arg Val Ala Val Asp Lys His Gln Ala Leu Leu Lys Ala Ala Met
635 640 645
Ser Gly Gln Gly Val Asp Arg His Leu Phe Ala Leu Tyr Ile Val
650 655 660
Ser Arg Phe Leu His Leu Gln Ser Pro Phe Leu Thr Gln Val His
665 670 675
Ser Glu Gln Trp Gln Leu Ser Thr Ser Gln Ile Pro Val Gln Gln
680 685 690
Met His Leu Phe Asp Val His Asn Tyr Pro Asp Tyr Val Ser Ser
695 700 705
Gly Gly Gly Phe Gly Pro Ala Asp Asp His Gly Tyr Gly Val Ser
710 715 720
Tyr Ile Phe Met Gly Asp Gly Met Ile Thr Phe His Ile Ser Ser
725 730 735
Lys Lys Ser Ser Thr Lys Thr Asp Ser His Arg Leu Gly Gln His
740 745 750
Ile Glu Asp Ala Leu Leu Asp Val Ala Ser Leu Phe Gln Ala Gly
755 760 765
Gln His Phe Lys Arg Arg Phe Arg Gly Ser Gly Lys Glu Asn Ser
770 775 780
Arg His Arg Cys Gly Phe Leu Ser Arg Gln Thr Gly Ala Ser Lys
785 790 795
Ala Ser Met Thr Ser Thr Asp Phe
800

<210> 13
<211> 295
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3360857CD1

<400> 13
Met Val Asp Ser Val Tyr Arg Thr Arg Ser Leu Gly Val Ala Ala
1 5 10 15
Glu Gly Leu Pro Asp Gln Tyr Ala Asp Gly Glu Ala Ala Arg Val
20 25 30
Trp Gln Leu Tyr Ile Gly Asp Thr Arg Ser Arg Thr Ala Glu Tyr
35 40 45
Lys Ala Trp Leu Leu Gly Leu Leu Arg Gln His Gly Cys Gln Arg
50 55 60
Val Leu Asp Val Ala Cys Gly Thr Gly Val Asp Ser Ile Met Leu
65 70 75

```
Val Glu Glu Gly Phe Ser Val Thr Ser Val Asp Ala Ser Asp Lys
                80                  85                  90
Met Leu Lys Tyr Ala Leu Lys Glu Arg Trp Asn Arg Arg His Glu
                95                  100                 105
Pro Ala Phe Asp Lys Trp Val Ile Glu Glu Ala Asn Trp Met Thr
                110                 115                 120
Leu Asp Lys Asp Val Pro Gln Ser Ala Glu Gly Gly Phe Asp Ala
                125                 130                 135
Val Ile Cys Leu Gly Asn Ser Phe Ala His Leu Pro Asp Cys Lys
                140                 145                 150
Gly Asp Gln Ser Glu His Arg Leu Ala Leu Lys Asn Ile Ala Ser
                155                 160                 165
Met Val Arg Ala Gly Gly Leu Leu Val Ile Asp His Arg Asn Tyr
                170                 175                 180
Asp His Ile Leu Ser Thr Gly Cys Ala Pro Pro Gly Lys Asn Ile
                185                 190                 195
Tyr Tyr Lys Ser Asp Leu Thr Lys Asp Val Thr Thr Ser Val Leu
                200                 205                 210
Ile Val Asn Asn Lys Ala His Met Val Thr Leu Asp Tyr Thr Val
                215                 220                 225
Gln Val Pro Gly Ala Gly Gln Asp Gly Ser Pro Gly Leu Ser Lys
                230                 235                 240
Phe Arg Leu Ser Tyr Tyr Pro His Cys Leu Ala Ser Phe Thr Glu
                245                 250                 255
Leu Leu Gln Ala Ala Phe Gly Gly Lys Cys Gln His Ser Val Leu
                260                 265                 270
Gly Asp Phe Lys Pro Tyr Lys Pro Gly Gln Thr Tyr Ile Pro Cys
                275                 280                 285
Tyr Phe Ile His Val Leu Lys Arg Thr Asp
                290                 295
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<210> 14
<211> 575
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 3449671CD1

<400> 14

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Met Thr Ser Lys Lys Leu Val Asn Ser Val Ala Gly Cys Ala Asp
 1              5                   10                  15
Asp Ala Leu Ala Gly Leu Val Ala Cys Asn Pro Asn Leu Gln Leu
                20                  25                  30
Leu Gln Gly His Arg Val Ala Leu Arg Ser Asp Leu Asp Ser Leu
                35                  40                  45
Lys Gly Arg Val Ala Leu Leu Ser Gly Gly Gly Ser Gly His Glu
                50                  55                  60
Pro Ala His Ala Gly Phe Ile Gly Lys Gly Met Leu Thr Gly Val
                65                  70                  75
Ile Ala Gly Ala Val Phe Thr Ser Pro Ala Val Gly Ser Ile Leu
                80                  85                  90
Ala Ala Ile Arg Ala Val Ala Gln Ala Gly Thr Val Gly Thr Leu
                95                  100                 105
Leu Ile Val Lys Asn Tyr Thr Gly Asp Arg Leu Asn Phe Gly Leu
```

```
                110                 115                 120
Ala Arg Glu Gln Ala Arg Ala Glu Gly Ile Pro Val Glu Met Val
                125                 130                 135
Val Ile Gly Asp Asp Ser Ala Phe Thr Val Leu Lys Lys Ala Gly
                140                 145                 150
Arg Arg Gly Leu Cys Gly Thr Val Leu Ile His Lys Val Ala Gly
                155                 160                 165
Ala Leu Ala Glu Ala Gly Val Gly Leu Glu Glu Ile Ala Lys Gln
                170                 175                 180
Val Asn Val Val Thr Lys Ala Met Gly Thr Leu Gly Val Ser Leu
                185                 190                 195
Ser Ser Cys Ser Val Pro Gly Ser Lys Pro Thr Phe Glu Leu Ser
                200                 205                 210
Ala Asp Glu Val Glu Leu Gly Leu Gly Ile His Gly Glu Ala Gly
                215                 220                 225

Val Arg Arg Ile Lys Met Ala Thr Ala Asp Glu Ile Val Lys Leu
                230                 235                 240
Met Leu Asp His Met Thr Asn Thr Thr Asn Ala Ser His Val Pro
                245                 250                 255
Val Gln Pro Gly Ser Ser Val Val Met Met Val Asn Asn Leu Gly
                260                 265                 270
Gly Leu Ser Phe Leu Glu Leu Gly Ile Ile Ala Asp Ala Thr Val
                275                 280                 285
Arg Ser Leu Glu Gly Arg Gly Val Lys Ile Ala Arg Ala Leu Val
                290                 295                 300
Gly Thr Phe Met Ser Ala Leu Glu Met Pro Gly Ile Ser Leu Thr
                305                 310                 315
Leu Leu Leu Val Asp Glu Pro Leu Leu Lys Leu Ile Asp Ala Glu
                320                 325                 330
Thr Thr Ala Ala Ala Trp Pro Asn Val Ala Ala Val Ser Ile Thr
                335                 340                 345
Gly Arg Lys Arg Ser Arg Val Ala Pro Ala Glu Pro Gln Glu Ala
                350                 355                 360
Pro Asp Ser Thr Ala Ala Gly Gly Ser Ala Ser Lys Arg Met Ala
                365                 370                 375
Leu Val Leu Glu Arg Val Cys Ser Thr Leu Leu Gly Leu Glu Glu
                380                 385                 390
His Leu Asn Ala Leu Asp Arg Ala Ala Gly Asp Gly Asp Cys Gly
                395                 400                 405
Thr Thr His Ser Arg Ala Ala Arg Ala Ile Gln Glu Trp Leu Lys
                410                 415                 420
Glu Gly Pro Pro Pro Ala Ser Pro Ala Gln Leu Leu Ser Lys Leu
                425                 430                 435
Ser Val Leu Leu Leu Glu Lys Met Gly Gly Ser Ser Gly Ala Leu
                440                 445                 450
Tyr Gly Leu Phe Leu Thr Ala Ala Ala Gln Pro Leu Lys Ala Lys
                455                 460                 465
Thr Ser Leu Pro Ala Trp Ser Ala Ala Met Asp Ala Gly Leu Glu
                470                 475                 480
Ala Met Gln Lys Tyr Gly Lys Ala Ala Pro Gly Asp Arg Thr Met
                485                 490                 495
Leu Asp Ser Leu Trp Ala Ala Gly Gln Glu Leu Gln Ala Trp Lys
                500                 505                 510
Ser Pro Gly Ala Asp Leu Leu Gln Val Leu Thr Lys Ala Val Lys
                515                 520                 525
Ser Ala Glu Ala Ala Ala Glu Ala Thr Lys Asn Met Glu Ala Gly
```

```
                530                     535                     540
Ala Gly Arg Ala Ser Tyr Ile Ser Ser Ala Arg Leu Glu Gln Pro
                545                     550                     555
Asp Pro Gly Ala Val Ala Ala Ala Ala Ile Leu Arg Ala Ile Leu
                560                     565                     570
Glu Val Leu Gln Ser
                575
```

<210> 15
<211> 180
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 5497787CD1

<400> 15

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Met Ala Ser Ser Val Gly Asn Val Ala Asp Ser Thr Glu Pro Thr
 1               5                  10                  15
Lys Arg Met Leu Ser Phe Gln Gly Leu Ala Glu Leu Ala His Arg
                20                  25                  30
Glu Tyr Gln Ala Gly Asp Phe Glu Ala Ala Glu Arg His Cys Met
                35                  40                  45
Gln Leu Trp Arg Gln Glu Pro Asp Asn Thr Gly Val Leu Leu Leu
                50                  55                  60
Leu Ser Ser Ile His Phe Gln Cys Arg Arg Leu Asp Arg Ser Ala
                65                  70                  75
His Phe Ser Thr Leu Ala Ile Lys Gln Asn Pro Leu Leu Ala Glu
                80                  85                  90
Ala Tyr Ser Asn Leu Gly Asn Val Tyr Lys Glu Arg Gly Gln Leu
                95                 100                 105
Gln Glu Ala Ile Glu His Tyr Arg His Ala Leu Arg Leu Lys Pro
               110                 115                 120
Asp Phe Ile Asp Gly Tyr Ile Asn Leu Ala Ala Ala Leu Val Ala
               125                 130                 135
Ala Gly Asp Met Glu Gly Ala Val Gln Ala Tyr Val Ser Ala Leu
               140                 145                 150
Gln Tyr Asn Pro Asp Leu Tyr Cys Val Arg Ser Asp Leu Gly Asn
               155                 160                 165
Leu Leu Lys Ala Leu Gly Arg Leu Glu Glu Ala Lys Val Gly Val
               170                 175                 180
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<210> 16
<211> 2120
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1632930CB1

<400> 16

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gatggcggag gacagcgagt ctgcggccag ccagcagagc ctggaactgg acgaccagga  60
cacgtgcggg atagacgggg acaatgagga ggagacggag cacgccaaag gaagtcctgg 120
```

agggtatttg ggagccaaaa agaaaaagaa gaaacagaag agaaaaaagg agaaaccaaa 180
ttccggaggc accaagtcag actcggcatc tgattcccag gagattaaaa ttcagcagcc 240
ttcgaaaaat cccagtgttc caatgcagaa gttgcaggat atccagagag caatggagct 300
gctatccgca tgccagggcc cagccaggaa cattgatgag gctgcaaagc acagatacca 360
gttttgggac acacaaccgg taccaaaact agatgaagtc ataacatctc atggtgcaat 420
tgaaccagat aaagtcaacg tacggcaaga accgtattct ttgccacagg gttttatgtg 480
ggacacttta gacttgagtg atgccgaagt gctcaaggag ttatacacgt tgttaaatga 540
gaattacgta gaagatgatg acaatatgtt ccgatttgac tattcacccg agttcctgtt 600
gtgggctctg cgtccaccag gctggctcct gcagtggcac tgtggggtca gagtgtcttc 660
aaataaaaaa ctggtcggt tcataagtgc catcccagca aacattcgga tttatgacag 720
tgtgaagaag atggtagaaa tcaactttct ttgtgttcat aagaagttga gatcgaaacg 780
ggtagcccca gtgctaatcc gagagatcac tagaagagtg aacctggaag ggatcttcca 840
ggctgtgtac accgcgggag tggttcttcc taagcccata gccacatgca gatactggca 900
tcgatcacta aaccccagaa aattggtaga agtgaaattt tctcacttga gtagaaatat 960
gactttacag agaacaatga agctatacag acttccagat gttacaaaga cttcaggttt 1020
gagaccaatg gaaccaaaag atatcaaatc agttcgagaa ttaatcaaca cttacctgaa 1080
gcagtttcat ctggctccag tgatggatga agaggaagta gcccactggt tcctcccccg 1140
ggagcacatt attgacacgt ttgtagtgga gagccccaac ggtaaactga ctgatttcct 1200
gagcttctat acgctcccct ccacggtgat gcaccaccct gctcacaaga gcctcaaagc 1260
cgcctactca ttctacaaca tccacacaga gacgcccctg ctggacctca tgagcgacgc 1320
gctcatcctg gctaaatcga aaggatttga tgtattcaat gcactggatt tgatggaaaa 1380
taagacattc ttggaaaaac tcaagtttgg tataggagat ggcaatttgc agtattacct 1440
gtacaattgg aggtgtccag gtacagattc tgaaaaggtt ggactagtac tacaatagat 1500
ggatattttt atttctagaa ctctgacatc atcatttgtt aatatttaat gatttctgga 1560
actgccattc caaagaagaa taaaagcaca actcaagtga aattgaagta gtcgataatc 1620
agaaaagatg acaaaagtcc acatgtgaca tttgtacgtt tctagctaga atgttaaact 1680
tcatcctttt tttactgttg acctatttgt gggagggatg aaaggctaca aagagcacat 1740
tcttgtaatt ttcaaatttt tgcctgtctc ttgaagaggt attttttcac ccttagaaaa 1800
gggactgttt ttctatggac taagtagaag ttacagagtc atgtaagaaa atctttgcta 1860
ttgtgtggag agaaattgct gcatttctgt ttcttaagtg atggtacatt tgtccatgta 1920
acagaacaaa agatccattt ggaaattttt tttactggta tcaccttaca tggtatcact 1980
gggaacattt atggaatcaa cacttctgta gctcagtgac aggtggtggt tgtttaagtg 2040
cagagcaata ttaaaatgta ctggtgacta gtacatgtat ttctccataa gcagagttgc 2100
cgaatcaata aacatgcaat 2120

<210> 17
<211> 1559
<212> DNA
<213> Homo sapiens

<<220>
<221> misc_feature
<223> Incyte ID No: 2682663CB1

<400> 17
gcagccgtct acccggtgtc gcgttctgtg ttgtggcggc cctggatccg gcgtcagggc 60
gaccgggcgg acgaggtgga gccagagtct gtcaggcggg ttggtgaagg gcgcggggcc 120
gggcacggcg ttgggagtgc gcggcaggga ccggccaggc gggctgcagg cacctcagag 180
cccgggacac cccctcaacg tccgcaggcg cgatgaaggc actgatctta gtgggggggct 240
atgggacgcg gctacggccg ctgacgctga gcaccccgaa gccactggtg gacttctgca 300
ataagcccat cttgctgcac caagtggagg cgctagccgc ggcaggcgtg gaccacgtga 360
tcctggccgt gagctacatg tcgcaggtgc tggagaagga aatgaaggca caggagcaga 420
ggctgggaat ccgaatctcc atgtcccatg aagaggagcc tttggggaca gctgggcccc 480
tggcgctggc ccgtgaccta ctctctgaga ctgcagaccc tttcttcgtc ctcaacagtg 540
acgtgatctg cgatttcccc ttccaagcca tggtgcagtt ccaccggcac catggccagg 600
agggctccat cctggtgacc aaggtggagg aaccctccaa gtacggtgtg gtggtgtgtg 660

aggctgacac aggccgcatt caccggttcg tggagaagcc acaggtgttt gtgtccaata 720
agatcaacgc aggcatgtac atcctgagcc ctgcagtgct gcggcgcatc cagctgcagc 780
ctacgtccat tgagaaggag gtcttcccca ttatggccaa ggaggggcag ctatatgcca 840
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Lys Ala Ile Glu Leu Phe Ser Val Gly Gln Gly Pro Ala Lys Thr
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Glu Asn Ile Ile Asp Thr Phe Val Val Glu Asn Ala Asn Gly Glu
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Val Thr Asp Phe Leu Ser Phe Tyr Thr Leu Pro Ser Thr Ile Met
380 385 390
Asn His Pro Thr His Lys Ser Leu Lys Ala Ala Tyr Ser Phe Tyr
395 400 405
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425 430 435
Asp Leu Met Glu Asn Lys Thr Phe Leu Glu Lys Leu Lys Phe Gly
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Thr Cys Ser Gln Glu Thr Glu Pro Leu Gly Thr Ala Gly Pro Leu
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Ala Leu Ala Arg Asp Lys Leu Leu Asp Gly Ser Gly Glu Pro Phe
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Phe Val Leu Asn Ser Asp Val Ile Ser Glu Tyr Pro Leu Lys Glu
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Pro Ser Val Leu Asp Lys Ile Glu Leu Arg Pro Thr Ser Ile Glu
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Lys Glu Thr Phe Pro Lys Ile Ala Ala Ala Gln Gly Leu Tyr Ala
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Met Val Leu Pro Gly Phe Trp Met Asp Ile Gly Gln Pro Arg Asp
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Tyr Ile Thr Gly Leu Arg Leu Tyr Leu Asp Ser Leu Arg Lys Lys
230 235 240
Ser Pro Ala Lys Leu Thr Ser Gly Pro His Ile Val Gly Asn Val
245 250 255
Leu Val Asp Glu Thr Ala Thr Ile Gly Glu Gly Cys Leu Ile Gly
260 265 270
Pro Asp Val Ala Ile Gly Pro Gly Cys Ile Val Glu Ser Gly Val
275 280 285
Arg Leu Ser Arg Cys Thr Val Met Arg Gly Val Arg Ile Lys Lys
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His Ala Cys Ile Ser Ser Ser Ile Ile Gly Trp His Ser Thr Val
305 310 315
Gly Gln Trp Ala Arg Ile Glu Asn Met Thr Ile Leu Gly Glu Asp
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Val Ser Tyr Arg Ala Glu Gln Leu Glu Gln Glu Met Thr Val His
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Ala Asp Arg Leu Gly Val Lys Leu Ile Phe Ser Leu Glu Glu Glu
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Pro Leu Gly Thr Ala Gly Pro Leu Ala Leu Ala Arg Lys His Leu
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Asp Phe Pro Phe Lys Gln Met Val Glu Phe His Lys Asn His Gly

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Phe Val Glu Lys Pro Gln Glu Tyr Val Gly Asn Lys Ile Asn Ala
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Gly Leu Tyr Ile Phe Ser Ser Lys Ile Leu Asp Arg Ile Pro Leu
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Lys Pro Thr Ser Ile Glu Lys Glu Ile Phe Pro Glu Met Ala Phe
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Ser Gly Asn Leu Tyr Ala Phe Val Leu Pro Gly Phe Trp Met Asp
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Val Gly Gln Pro Lys Asp Phe Leu Lys Gly Met Ser Leu Phe Leu
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His Ser Thr Ile Leu Ser Asp Ser Ser Ile Gly Asn Tyr Ser Trp
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Val Ser Gly Ser Ile Val Gly Arg Lys Cys His Ile Gly Ser Trp
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Lys Asp Glu Leu Tyr Leu Asn Gly Ala Ser Val Leu Pro His Lys
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